

Observational study of chronic myeloid leukemia Italian patients who discontinued tyrosine kinase inhibitors in clinical practice



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ABSTRACT

It is judged safe to discontinue treatment with tyrosine kinase inhibitors (TKI) for chronic myeloid leukemia (CML) in experimental trials on treatment-free remission (TFR). We collected a total of 293 Italian patients with chronic phase CML who discontinued TKI in deep molecular response. Seventy-two percent of patients were on treatment with imatinib, and 28% with second generation TKI at the time of discontinuation. Median duration of treatment with the last TKI was 77 months [Interquartile Range (IQR) 54;111], median duration of deep molecular response was 46 months (IQR 31;74). Duration of treatment with TKI and duration of deep molecular response were shorter with second generation TKI than with imatinib ($P < 0.001$). Eighty-eight percent of patients discontinued as per clinical practice, and reasons for stopping treatment were: toxicity (20%), pregnancy (6%), and shared decision between treating physician and patient (62%). After a median follow up of 34 months (range, 12-

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161) overall estimated TFR was 62% (95%CI: 56;68). At 12 months, TFR was 68% (95%CI: 62;74) for imatinib, 73% (95%CI: 64;83) for second generation TKI. Overall median time to restart treatment was six months (IQR 4;11). No progressions occurred. Although our study has the limitation of a retrospective study, our experience within the Italian population confirms that discontinuation of imatinib and second generation TKI is feasible and safe in clinical practice.

Introduction

Chronic myeloid leukemia (CML) patients have reached a near-normal life expectancy thanks to tyrosine kinase inhibitors (TKI).^{1,2} These drugs, however, can cause several persistent low-grade side effects that affect quality of life, and can be associated in the long term with severe toxicities.³ For this lifelong disease, tolerance and adherence to treatment are an issue. Furthermore, thanks to the success of the therapies, patients grow older and accumulate comorbidities that require concomitant treatments that can possibly interfere with TKI. Younger patients have other problems because living with TKI interferes with family planning, availability for the job market, life insurance, and so on.⁴ Besides, as more and more patients are living with their disease, high treatment costs are becoming an important issue.⁵

Over recent years, several papers have reported on treatment discontinuation in CML patients in persistent deep molecular response (DMR).⁶⁻²⁵ The majority of these studies have reported on patients who had achieved a DMR with imatinib. There are fewer data reported on the discontinuation of second generation TKI, and with a shorter follow up. The definitions of DMR and the criteria for treatment discontinuation, for molecular relapse, and for treatment resumption, varied among these studies. Therefore, the reported treatment-free remission (TFR) rate ranged widely (between 30% and 70%), with the first reports mostly showing a TFR rate of approximately 40%; more recent reports, which adopted less stringent criteria for treatment discontinuation and therapy resumption, showed a TFR rate of approximately 60%. Partly due to these different definitions, it is still difficult to identify the factors that may predict for the TFR rate, although some analyses have drawn attention to the predictive value of treatment duration, Sokal score, duration of molecular response (MR), and response to first-line TKI treatment. Prior studies were mostly academic or company-sponsored; these were mostly prospective in nature, with restricted and carefully selected inclusion criteria. Nowadays, doctors and patients are willing and ready to introduce TKI discontinuation in clinical practice. Very few data are available on the effects and the outcome of treatment discontinuation outside prospective studies and without a central control of MR. We report here on 293 adult patients who discontinued TKI outside studies, as per clinical practice.

Methods

Study design and purpose

We designed a retrospective observational study of Italian patients with Philadelphia positive (Ph⁺) CML in chronic phase who had discontinued TKI treatment in DMR, with a follow up after discontinuation over one year. All hematology centers

belonging to the Italian Group for the Hematologic Diseases of the Adults (GIMEMA) were invited to participate; thirty-two centers contributed to this study. The primary end point of the study was the TFR rate after one year from TKI treatment discontinuation. Secondary end points included: longer-term TFR status, safety (including the outcome after treatment resumption and disease progression), identifying factors associated with MR. Data on the main disease characteristics were collected for each patient. These were: all treatments before and after discontinuation, duration of each treatment, response to each treatment, and the reasons for discontinuation. The cutoff date for this analysis was February 2017. The observational retrospective study protocol was approved by the ethics committees of all centers taking part.

Response definitions and statistical analysis

Molecular response was assessed by quantitative polymerase chain reaction (qPCR) according to the standard methodology;²⁶ all analyses were performed by the GIMEMA Laboratories Network (LabNet) for CML, expressed according to the International Scale. Major molecular response (MMR) was defined as a BCR-ABL1 ratio ≤ 0.1 with at least 10,000 ABL1 copies. Deep molecular response was defined as MR4 (BCR-ABL1 ratio $\leq 0.01\%$ with at least 10,000 ABL1 copies), or MR4.5 (BCR-ABL1 ratio $\leq 0.0032\%$ with at least 32,000 ABL1 copies), or MR5 (BCR-ABL1 ratio $\leq 0.001\%$ with at least 100,000 ABL1 copies) confirmed at least three times before TKI discontinuation.²⁶ In a few patients who discontinued TKI before the establishment of molecular standardization, DMR was defined as a level of BCR-ABL1 transcript undetectable by qPCR or by qualitative PCR, confirmed in at least two controls. The cytogenetic response was assessed according to European LeukemiaNet (ELN) criteria.²⁷

Treatment-free response was assessed using the Kaplan-Meier method, from the date of TKI discontinuation to the date documenting the restart of therapy regardless of the reason. In fact, since this is a retrospective study, criteria for treatment resumption have not been pre-established. TFR was estimated using a Kaplan-Meier curve and 95% confidence interval (CI). Deaths were considered as censored events. For all the other patients, data were censored at the date of last qPCR.

Continuous data were expressed as medians with interquartile ranges (IQR, i.e. 25th and 75th percentiles) as a measure of variability. A Mann-Whitney U test was used for comparison of quantitative variables and χ^2 or Fisher exact test was used for categorical variables as appropriate.

Clinical and biological variables at baseline were assessed as potential independent prognostic factors for MR by univariate analysis using Cox regression model. Variables were entered without any transformation or cut off.

For the multivariate analysis, a stepwise backward selection procedure was carried out.²⁸ The non-linear effect of continuous covariates was modeled using a restrictive cubic spline function, and its significance was assessed using the Wald test; similar methods were used to check interactions.²⁹ The best fitting model was chosen according to the Akaike information criterion.

$P=0.05$ was considered statistically significant. All analyses were carried out using R v.3.3.3 statistical software.³⁰

Results

Patients

We collected data on 293 patients who discontinued TKI between June 2003 and February 2016. Overall, 34 of 293 patients (11.5%) suspended treatment because they were enrolled in the prospective interventional Imatinib Suspension and Validation (ISAV) study.¹⁵ All the other patients discontinued as per clinical practice, and the rea-

sons were: toxicity (20%, 58 of 293), pregnancy (6%, 17 of 293), and a shared decision between the treating physician and the patient (62%, 182 of 293). Finally, one patient discontinued the TKI because of chemotherapy for another neoplasia. Reason of discontinuation was not known for one patient.

Patients' characteristics are reported in Table 1. Median age was 49 years (IQR 38-60) at diagnosis and 59 years (IQR 48-70) at discontinuation. At the time of discontinu-

Table 1. Patients' baseline characteristics.

	Imatinib	2 nd generation TKI	Overall	P
N	211	82	293	
Age at diagnosis (median [IQR])	47 [36, 58]	55 [45, 67]	49 [38, 60]	0.001
Age at discontinuation (median [IQR])	58 [46,67]	63 [51, 74]	59 [48, 70]	0.023
Sex				0.884
Males (%)	117 (56)	44 (54)	161 (55)	
Sokal Score n=263 (%)				0.346
Low	114 (61)	40 (52)	154 (59)	
Intermediate	52 (28)	28 (36)	80 (30)	
High	20 (11)	9 (12)	29 (11)	
Type of transcript n=252 (%)				0.126
b2a2	42 (23)	20 (29)	62 (24.5)	
b2a3	0 (0)	1 (1.5)	1 (0.5)	
b3a2	141 (76.5)	46 (68)	187 (74)	
b3a3	1 (0.5)	0 (0)	1 (0.5)	
e1a2	0 (0)	1 (1.5)	1 (0.5)	
Last TKI (%) n=293				<0.001
Imatinib	211 (100)	0 (0)	211 (72)	
Nilotinib	0 (0)	58 (71)	58 (19.5)	
Dasatinib	0 (0)	23 (28)	23 (8)	
Bosutinib	0 (0)	1 (1)	1 (0.5)	
Line of treatment at discontinuation (%) n=293				<0.001
1 st line	129 (61)	33 (40)	162 (55)	
2 nd line	81 (38.5)	36 (44)	117 (40)	
3 rd line	1 (0.5)	12 (15)	13 (4.5)	
4 th line	0 (0)	1 (1)	1 (0.5)	
Reasons for discontinuation (%) n=292				<0.001
Shared decision	135 (64)	47 (57)	182 (62)	
Toxicity	28 (13.5)	30 (37)	58 (20)	
ISAV13	34 (16)	0 (0)	34 (11.5)	
Pregnancy	12 (6)	5 (6)	17 (6)	
Chemotherapy for 2nd tumor	1 (0.5)	0 (0)	1 (0.5)	
MR at discontinuation (%) n=290				0.315
MR4	70 (33)	31 (38)	101 (35)	
MR4.5	61 (29)	29 (36)	90 (31)	
MR5	41 (20)	12 (15)	53 (18)	
Transcript undetectable	37 (18)	9 (11)	46 (16)	
Duration of last TKI (median [IQR])	96 [62, 120]	50 [32, 66]	77 [54, 111]	<0.001
Duration of treatment with any TKI (median [IQR])	96 [62, 120]	73 [51, 98]	87 [59, 117]	0.002
Duration of total treatment (median [IQR])	104 [73, 142]	76 [52, 109]	98 [65, 133]	<0.001
Time to DMR (median [IQR])	24 [12, 52]	13 [6, 26]	21 [10, 42]	<0.001
Duration of DMR (median [IQR])	53 [33, 82]	36 [25, 46]	46 [30, 73]	<0.001

IQR: interquartile ranges; TKI: tyrosine kinase inhibitor; MR: molecular response; DMR: deep molecular response.

ation, 211 patients (72%) were on treatment with imatinib and 82 patients (28%) with either nilotinib (n=58), dasatinib (n=23), or bosutinib (n=1). There were no differences in age, sex, Sokal score and type of transcript between imatinib and second generation TKI. One hundred and sixty-two patients (55%) discontinued in first line, 117 patients (40%) in second line, 13 patients (4.5%) in third line, and one patient in fourth line. Among those who discontinued imatinib, 73 patients (35%) had been pre-treated with α -interferon (IFN) and seven patients had been submitted to allogeneic stem cell transplantation. Median duration of treatment with any TKI was 87 months (IQR 59-117) for all patients, 96 months (IQR 62-120) for imatinib patients, and 73 (IQR 51-98) months for second generation TKI patients ($P=0.002$). Median duration of treatment with the last TKI was 77 months (IQR 54-111) for all patients, and 50 months (IQR 32; 66) for second generation TKI patients. Median duration of DMR was 46 months (IQR 30-73) for all patients, 53 months (IQR 33-82) for imatinib patients, and 36 months (IQR 25-46) for second generation TKI patients ($P<0.001$). Overall, all patients but one had an optimal early response to last treatment. At three months of last TKI, 34% of patients were in MMR, 40% were in CCyR and/or had a transcript $\leq 1\%$, and 25% were in PCyR and/or had a transcript $\leq 10\%$.

At treatment discontinuation the response was as follows: undetectable transcript in 16% of patients, MR4 in 35% of patients, MR4.5 in 31% of patients, and MR5 in 18%. There was no difference in the grade of molecular response at discontinuation between patients on imatinib and patients on second generation TKI ($P=0.315$).

Relapses and treatment-free remission

At 12 months, the estimated TFR was 69% (95%CI: 64-75) for all patients (Figure 1A), 68% (95%CI: 62-74) for imatinib patients (Figure 1B), 73% (95%CI: 64-83) for second generation TKI patients (Figure 1C).

Median follow up was 34 months (IQR 24-53) for all patients, 42 months (IQR 26-56) for imatinib patients, and 26 months (IQR 21-34) for second generation TKI patients. At median follow up, TFR was 62% (95%CI: 56-68) for all patients (at 34 months), 60% (95%CI: 54-67) for imatinib patients (at 42 months), 67% (95%CI: 57-78) for second generation TKI patients (at 26 months) (Figure 1). There was no significant difference in TFR between patients who had discontinued imatinib first-line *versus* imatinib after IFN *versus* further lines ($P=0.35$), and there was no difference in TFR between patients who discontinued second generation TKI frontline (n=33) *versus* second-line for intolerance (n=30) *versus* second-line for resistance (n=16) ($P=0.16$).

Overall, 114 patients (39%) resumed treatment. Reasons for resuming were: loss of MR4 (19%), loss of MMR (70%), loss of CCyR (9%), other (2%). The reasons for restarting imatinib and second generation TKI were similar ($P=0.13$). Overall median time to restart treatment was six months (IQR 4-11). Although 75% of patients had restarted treatment by the end of the first year, the last treatment resumption was after 105 months of TFR. Median time to loss of MR4 was three months (IQR 2-7); median time to loss of MMR was four months (IQR 3-7), and median time to loss of CCyR was five months (IQR 4-6). Median time from loss of response to restarting treatment was one month (IQR 0-2).

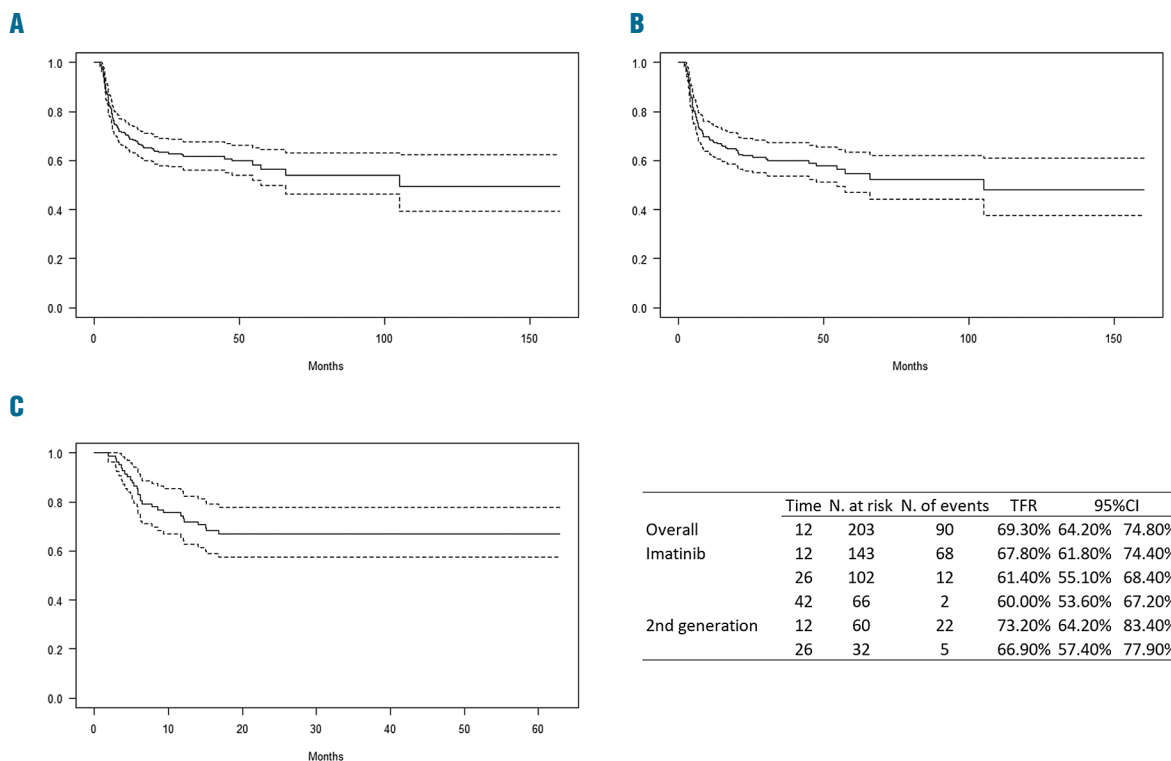


Figure 1. Kaplan-Meier curves for Italian patients who discontinued tyrosine kinase inhibitor (TKI). (A) Overall population. (B) Patients who discontinued imatinib. (C) Patients who discontinued second generation TKI. Estimated treatment-free remission (TFR) is reported at 12 months for the overall population; at 12, 26 (median follow up for patients who discontinued second generation TKI), and 42 (median follow up for patients who discontinued imatinib) months for imatinib; at 12 and 26 months (median follow up for patients who discontinued second generation TKI) for second generation TKI. N: number.

No progressions occurred. Nine deaths were reported but none of them was disease related.

The patients who resumed therapy (Table 2) were given imatinib (n=77), nilotinib (n=22), dasatinib (n=9), bosutinib (n=3), ponatinib (n=1), or IFN (n=2). Most of the patients who stopped imatinib restarted imatinib after relapse, and patients who were on second generation TKI mainly stayed with second generation TKI. Ninety-four percent of the patients who were retreated achieved at least another MMR, and 82% of them achieved another DMR, fitting the criteria for a second attempt at discontinuation.³¹

In 20 patients who had lost MR4, and in four patients who had lost MMR, the treatment was not resumed fol-

lowing a shared decision with the doctor. Interestingly, they were still on the same response after a median time of 12 months (IQR 1-32).

Prognostic factors

Univariate analysis – Univariate analysis was used to assess age (considered as continuous variable), sex (female vs. male), Sokal score (intermediate vs. low; high vs. low), type of therapy (second generation TKI vs. imatinib), line of therapy at stop (imatinib vs. imatinib post IFN; first-line second generation vs. second generation in second or further lines), type of transcript (b2a2 vs. others), duration of therapy with the last TKI and any TKI (continuous variables), duration of total treatment (continuous

Table 2. Type of retreatment after failure of discontinuation.

	Overall (n=114)	2nd generation TKI (n=26)	Imatinib (n=88)
Type of retreatment (%)			
Imatinib	77 (67)	2 (8)	75 (85)
Nilotinib	22 (19)	18 (69)	4 (5)
Dasatinib	9 (8)	4 (15)	5 (6)
Bosutinib	3 (3)	1 (4)	2 (2)
Ponatinib	1 (1)	1 (4)	0 (0)
IFN α	2 (2)	0 (0)	2 (2)

Table 3. Hazard Ratios (HRs) computed at univariate analysis.

	HR	95%CI	P	
Sex				
female vs. male	1.17	0.81	1.69	0.41
Sokal score				
Intermediate vs. low	0.74	0.47	1.17	0.19
high vs. low	1.66	0.98	2.81	0.06
Type of therapy				
2 nd generation vs. imatinib	0.8	0.52	1.23	0.31
Type of transcript				
b2a2 vs. others	0.93	0.58	1.49	0.77
Age at discontinuation (older vs. younger; diff. of 22 ys)	0.76	0.58	0.98	0.04
Duration of DMR* (diff. of 43 mos)	1.01	0.77	1.31	0.97
Time to DMR before stop* (32 mos increase)	0.97	0.75	1.27	0.84
Duration of therapy with last TKI* (57 mos increase)	1.04	0.80	1.37	0.73
Duration of treatment with any TKIs* (58 mos increase)	0.85	0.64	1.13	0.27
Duration of total treatment* (68 mos increase)	0.79	0.62	1.02	0.07
Depth of MR at stop				
MR4.5 vs. MR4	0.67	0.42	1.07	0.1
MR5 vs. MR4	0.68	0.4	1.14	0.14
Undetectable vs. MR4	0.7	0.4	1.19	0.18
Line of therapy at stop				
1 st line vs. \geq 2 nd line	1.53	1.04	2.24	0.03
Reason for discontinuation				
Pregnancy vs. shared decision with MD	1.57	0.81	3.05	0.18
ISAV vs. shared decision with MD	1.40	0.82	2.38	0.22
Toxicity vs. shared decision with MD	0.73	0.43	1.21	0.22

*For each variable the difference of months between groups of patients considered for computing HR corresponds to the Interquartile Range (IQR); ys: years; DMR: deep molecular response; mos: months; MD: medical doctor.

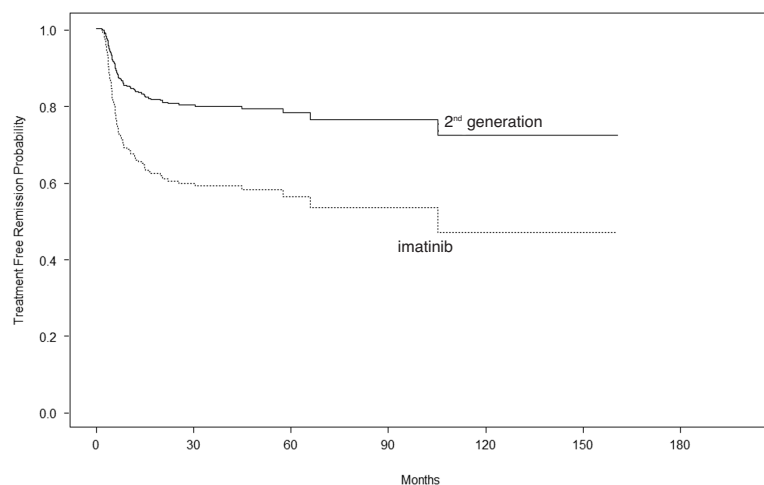


Figure 2. Tyrosine kinase inhibitor (TKI)-treatment-free remission (TFR) curves adjusted for age at discontinuation, Sokal score, line of therapy, and duration of disease.

Table 4. Median and Interquartile Range of duration of treatment in patients who discontinued treatment in first line or in second or further lines of therapy.

Lines of treatment at discontinuation	Duration of total treatment [median (IQR)]	P
1st Line	82 (60; 105)	<0.001
≥2nd Line	128 (86;169)	

IQR: Interquartile Ranges.

Table 5. Multivariate Cox regression analysis for restarting therapy. Figures reported are Hazard Ratios and 95% confidence intervals.

	HR	95%CI	P
Age at discontinuation (10 yrs difference)	0.84	0.73 - 0.97	0.02
Sokal score			
Intermediate vs. low	0.92	0.54 - 1.57	0.76
High vs. low	2.07	1.16 - 3.71	0.01
Line of therapy: 2 nd vs. 1 st line	0.80	0.50 - 1.30	0.37
2 nd generation TKIs vs. imatinib	0.43	0.20 - 0.91	0.03
Duration of total therapy (one yr increase) in patients treated with imatinib*	1.00	0.94 - 1.07	0.90
Duration of total therapy (one yr increase) in patients treated with 2 nd generation TKIs**	0.78	0.65 - 0.93	0.01

*HR = 1 expresses no risk increase associated to the increase of 1 year of the duration of therapy in patients treated with imatinib. ** HR < 1 expresses the risk reduction associated to the increase of 1 year of the duration of therapy in patients treated with 2nd generation tyrosine kinase inhibitor (TKI); yr: years; HR: Hazard Ratios; CI: Confidence Intervals.

variable), time to DMR and DMR duration (continuous variables), depth of MR at stop (MR4.5 vs. MR4, MR5 vs. MR4 and Undetectable vs. MR4), reasons for discontinuation (pregnancy, ISAV study and toxicity vs. shared decision with medical doctor). The only statistically significant risk factors that affected TFR were age at discontinuation (with a higher risk for younger patients) and line of treatment (Table 3). When we assessed the duration of total treatment for patients who discontinued TKI in front line versus second line, we observed that patients who discontinued treatment front line had a significantly shorter duration of treatment ($P < 0.001$) (Table 4).

Multivariate analysis - The line of treatment lost statistical significance in a multivariate analysis including age at discontinuation, Sokal score, duration of total treatment, line of treatment, and type of TKI at discontinuation (Table 5). Patients treated with second generation TKI showed a better TFR (HR 0.43; 95%CI: 0.20-0.91) (Table 5 and Figure 2). Duration of total treatment was positively

associated with TFR among patients treated with second generation TKI with a 22% risk reduction for one additional year of treatment (HR: 0.78; 95%CI: 0.65-0.93).

Discussion

Although at present no guidelines explicitly recommend treatment discontinuation, this study showed that many physicians have already experienced TKI cessation in their clinical practice because of intolerance, toxicity, and patient desire to stop the treatment. This multi-center observational study has confirmed that treatment cessation was safe as no progression occurred and the overall TFR was 69% at 12 months, consistent with data reported in previous studies.^{6,25} After discontinuation, patients were monitored with the same frequency as in the EURO-SKI study: most of the patients had a molecular evaluation every month for the first six months, every six weeks for

the subsequent six months, and then every three months.²¹ Although we may think that a stringent monitoring is protective, and indeed most of the relapses occurred during the first year, late relapses were not complicated by loss of complete hematologic remission or progression to advanced phases, even if monitoring was less frequent.³² Given this, we must mention that Italian centers rely on the Lab-net CML network, which ensures a standardized measurement of minimal residual disease, with a short turn-around time between sampling and reporting.

The history of CML has been revolutionized by the introduction of imatinib, and while this has resulted in an extraordinary improvement in survival, second generation TKI have refined our concept of CML. The achievement of higher rates of DMR in shorter periods of time switched the goal of CML treatment from survival to cure, to the point that TFR was included in the data sheet of nilotinib.³³ However, for the moment, a definitive treatment discontinuation is not yet an option for everybody. All the studies have tried to define prognostic factors for a successful TFR in order to increase the number of patients who can experience a successful discontinuation. In our study, having a high Sokal risk score at diagnosis was predictive for a worse outcome, in agreement with the STIM and the Korean studies.^{7,16} As in the ISAV trial,¹⁵ we showed that age might have a role in the maintenance of response, with an advantage for older patients. We retrospectively observed that our population was almost entirely characterized by an optimal early response at three months; this could explain why TFR was comparable when discontinuation occurred in a first-line setting or during subsequent lines of therapy. Duration of treatment was reported as a prognostic factor in many studies.^{7,15,16,21} In our analysis, the duration of total treatment for patients who discontinued TKI in second line was significantly longer compared to patients who discontinued TKI in front-line (128 vs. 82 months). This could possibly account for the lower risk of relapses in patients who discontinued TKI in second line as shown in the univariate analysis. In fact, in the multivariate analyses, the line of treatment lost significance. In our study, the total duration of treatment had a positive influence particularly on patients treated with second generation TKI: we observed a 22% reduction of the risk of resuming therapy per year of treatment.

In this study, we observed that patients who discontinued second generation TKI had a median duration of treatment with the last TKI of 50 months *versus* 96 months of treatment with imatinib (Table 1). The results are in line with those of several prospective studies, such as the ENEST Freedom, the ENESStop (median duration of treatment with nilotinib of 43 months and 53 months, respectively), and the EURO-SKI trials (median duration of treatment with imatinib of 91 months).^{20,21,25} Furthermore, the multivariate Cox proportional hazards regression model showed a better probability of TFR for patients treated with second generation TKI, with an estimated 57% relative risk reduction in favor of the second generation TKI. Even considering the quite large confidence interval, the minimum risk reduction is still 9%. These data are in keeping with the superiority of second generation TKI in deeply and rapidly reducing the level of disease.

Importantly, almost all the patients who were retreated regained at least MMR, and 82% regained the DMR criteria for a second discontinuation attempt, which has been recently proven to be feasible.³¹ In fact, Legros *et al.* reported that 35% of patients who had a second discontinuation attempt (median total time of treatment of 103 months) remained free from relapse at three years.³¹ Those who have eventually restarted treatment had nonetheless taken advantage of a treatment 'holiday' without meaningful risks.

Conclusions

This multicenter observational study included a substantial number of patients who were cared for in care institutes through clinical practice procedures, confirming that treatment discontinuation is safe and effective also outside controlled clinical trials. Taking into account all the evidence collected in the last ten years, we think that TKI discontinuation in patients in persistent DMR must be considered in routine clinical practice, as long as molecular monitoring is performed regularly in standardized laboratories, and in accordance with the criteria stated in the ESMO and NCCN recommendations.^{34,35}

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References

- Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *N Engl J Med.* 2017;376(10):917-927.
- Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol.* 2015;2(5):e186-193.
- Stegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia.* 2016;30(8):1648-1671.
- Narra RK, Flynn KE, Atallah E. Chronic Myeloid Leukemia-the Promise of Tyrosine Kinase Inhibitor Discontinuation. *Curr Hematol Malig Rep.* 2017;12(5):415-423.
- Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood.* 2013;121(22):4439-4442.
- Rousselot P, Huguet F, Rea D, et al. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. *Blood.* 2007;109(1):58-60.
- Etienne G, Guilhot J, Rea D, et al. Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia. *J Clin Oncol.* 2017;35(3):298-305.
- Ross DM, Branford S, Seymour JF, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood.* 2013;122(4):515-522.
- Rousselot P, Charbonnier A, Cony-Makhoul P, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol.* 2014;32(5):424-430.
- Takahashi N, Kyo T, Maeda Y, et al. Discontinuation of imatinib in Japanese patients with chronic myeloid leukemia. *Haematologica.* 2012;97(6):903-906.
- Thielen N, van der Holt B, Cornelissen JJ, et al. Imatinib discontinuation in chronic

- phase myeloid leukaemia patients in sustained complete molecular response: a randomised trial of the Dutch-Belgian Cooperative Trial for Haemato-Oncology (HOVON). *Eur J Cancer*. 2013;49(15):3242-3246.
12. Lee S-E, Choi SY, Bang J-H, et al. Predictive factors for successful imatinib cessation in chronic myeloid leukemia patients treated with imatinib. *Am J Hematol*. 2013; 88(6):449-454.
 13. Mori S, Vagge E, le Coutre P, et al. Age and dPCR can predict relapse in CML patients who discontinued imatinib: the ISAV study. *Am J Hematol*. 2015;90(10):910-914.
 14. Tsutsumi Y, Ito S, Ohigashi H, Shiratori S, Teshima T. Unplanned discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia. *Mol Clin Oncol*. 2016;4(1):89-92.
 15. Lee S-E, Choi SY, Song H-Y, et al. Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: the KID study. *Haematologica*. 2016;101(6):717-723.
 16. Yhim H-Y, Lee N-R, Song E-K, et al. Long-Term Outcomes after Imatinib Mesylate Discontinuation in Chronic Myeloid Leukemia Patients with Undetectable Minimal Residual Disease. *Acta Haematol*. 2016;135(3):133-139.
 17. Ferrero D, Cerrano M, Crisà E, Aguzzi C, Gai V, Boccadoro M. How many patients can proceed from chronic myeloid leukaemia diagnosis to deep molecular response and long-lasting imatinib discontinuation? A real life experience. *Br J Haematol*. 2017;176(4):669-671.
 18. Imagawa J, Tanaka H, Okada M, et al. Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial): a multicentre phase 2 trial. *Lancet Haematol*. 2015;2(12):e528-535.
 19. Rea D, Nicolini FE, Tulliez M, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. *Blood*. 2017;129(7):846-854.
 20. Hochhaus A, Masszi T, Giles FJ, et al. Treatment-free remission following front-line nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. *Leukemia*. 2017;31(7):1525-1531
 21. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19(6):747-757.
 22. Mahon FX, Nicolini FE, Noel MP, et al. Preliminary report of the STIM2 study: a multicenter stop imatinib trial for chronic phase chronic myeloid leukemia de novo patients on imatinib [abstract]. *Blood*. 2013; 122(21):654.
 23. Takahashi N, Tauchi T, Kitamura K, et al. Deeper molecular response is a predictive factor for treatment-free remission after imatinib discontinuation in patients with chronic phase chronic myeloid leukemia: the JALSG-STIM213 study. *In J Hematol*. 2018;107(2):185-193.
 24. Shah NP, Paquette R, Müller MC, et al. Treatment-free remission (TFR) in patients with chronic phase chronic myeloid leukemia (CMLCP) and in stable deep molecular response (DMR) to dasatinib: the Dasfree Study. *Blood*. 2016; 128(22):1895.
 25. Hughes TP, Boquimpani CM, Takahashi N, et al. Treatment-free remission in patients with chronic myeloid leukemia in chronic phase according to reasons for switching from imatinib to nilotinib: subgroup analysis from ENESTop. *Blood*. 2016; 128(22):792.
 26. Cross NC, White HE, Colomer D, et al. Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. *Leukemia*. 2015;29(5):999-1003.
 27. Baccarani M, Deininger MW, Rosti G, et al. LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.
 28. Sander Greenland, Rhian Daniel, Neil Pearce; Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. *Int J Epidemiol*. 2016;45(2):565-575.
 29. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. *Epidemiology (Sunnyvale)*. 2016;6(2).
 30. R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria
 31. Legros L, Nicolini FE, Etienne G, et al. Second tyrosine kinase inhibitor discontinuation attempt in patients with chronic myeloid leukemia. *Cancer*. 2017; 123(22):4403-4410.
 32. Kong JH, Winton EF, Heffner LT, et al. Does the frequency of molecular monitoring after tyrosine kinase inhibitor discontinuation affect outcomes of patients with chronic myeloid leukemia? *Cancer*. 2017;123(13):2482-2488.
 33. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000798/WC500034394.pdf
 34. Hochhaus A, Saussele S, Rosti G, et al. Chronic Myeloid Leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Ann Oncol*. 2017;28(suppl_4):iv41-iv51.
 35. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf