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

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Key-points

- TKI discontinuation is feasible in clinical practice. After a follow-up of 34 months 62% of 293 patients remained in TFR without progression;
- Duration of treatment with TKIs and duration of deep molecular remission were shorter with 2nd generation TKIs than with imatinib.

Abstract

It is judged safe to discontinue treatment with tyrosine kinase inhibitors for chronic myeloid leukemia in experimental trials on treatment free remission. We collected a total of 293 Italian patients with chronic phase chronic myeloid leukemia who discontinued tyrosine kinase inhibitors in deep molecular response. 72% of patients were on treatment with imatinib, 28% with second generation tyrosine kinase inhibitors at the time of discontinuation. Median duration of treatment with the last tyrosine kinase inhibitor was 77 months (IQR 54;111), median duration of deep molecular response was 46 months (IQR 31;74). Duration of treatment with tyrosine kinase inhibitors and duration of deep molecular response were shorter with 2nd generation tyrosine kinase inhibitors than with imatinib ($p<0.001$). 88% of the Italian patients discontinued per clinical practice and reasons for stopping treatment were: toxicity for 20% of patients, pregnancy for 6% patients and shared decision between treating physician and patient for 62% of cases. After a median follow-up of 34 months (Min-Max 12-161) overall estimated treatment free remission was 62% (95% CI 56;68). At 12 months treatment free remission was 68% (95% CI 62;74) for imatinib, 73% (95% CI 64;83) for 2nd generation tyrosine kinase inhibitors. Overall median time to restart treatment was 6 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 2nd generation tyrosine kinase inhibitors is feasible and safe in the 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 a lifelong lasting disease, tolerance and adherence to treatment are an issue. Furthermore, thanks to the successful therapies, patients grow older and accumulate comorbidities that require concomitant treatments with possible interference with TKIs. Younger patients have other problems because living with TKIs interferes with family planning, with job availability, 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]

In the last years several papers have reported on the 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. Less data have been reported on the discontinuation of second generation TKIs, 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 about 40%, and the more recent ones, which employed less stringent criteria for treatment discontinuation and therapy resumption, of about 60%. Partially due to these different definitions, at present it is still difficult to identify the factors that may predict for the TFR rate, although some analyses have called attention on the predictive value of treatment duration, Sokal score, molecular response (MR) duration and response to first line TKI treatment. Prior studies were mostly academic or company-sponsored, and prospective, 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 molecular response. We report here on the cases of 293 adult patients who discontinued TKIs 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 and with a follow-up after

discontinuation longer than 1 year. All the Hematological Centers that belong 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 endpoint of the study was the TFR rate after one year from TKI treatment discontinuation. Secondary endpoints included: longer-term TFR status, safety (including the outcome after treatment resumption and disease progression), search for factors associated with molecular relapse. Data on the main disease characteristics, on all the treatments before and after discontinuation, on the duration of each treatment, on the response to each treatment, on the reasons for discontinuation, were collected for each patient. The cutoff date for this analysis was February 2017. The observational retrospective study protocol was approved by the Ethic Committees of all contributing Centers.

Response definitions and statistical methods

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 in 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 few patients who discontinued TKIs 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 ELN criteria.[27]

TFR was assessed using the Kaplan-Meier method, from the date of TKI discontinuation to the date documenting the re-initiation of therapy regardless of the reason. In fact, since this is a retrospective study, criteria for treatment resumption were not pre-established. TFR was estimated using 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 (IQRs, i.e. 25^{th} and 75^{th} percentiles) as a measure of variability. A Mann-Whitney U test was used for comparison of quantitative variables and Chi-square or Fisher's exact test was used for categorical variables as appropriate.

Clinical and biological variables at baseline were assessed as potential independent prognostic factors for molecular relapse by univariate analysis using Cox regression model. Variables were

entered without any transformation or cutting off.

For the multivariate analysis a stepwise backward selection procedure was carried out.[28] The nonlinear effect of continuous covariates was modeled using a restrictive cubic spline function and its significance was assessed using the Wald test; interactions were checked similarly.[29] The best fitting model was chosen according to the Akaike information criterion.

Significance level was set at 0.05. Analyses were carried out using R v 3.3.3 statistical software.[30]

Results

Patients

We collected data on 293 patients who discontinued TKIs between June 2003 and February 2016. Overall, 34 out of 293 patients (11.5%) suspended treatment because they were enrolled in the prospective interventional "Imatinib Suspension and Validation (ISAV)" study.[13] All the other patients discontinued per clinical practice, and reasons were: toxicity in 20% of patients (58/293), pregnancy in 6% of patients (17/293), and a shared decision between the treating physician and the patient in 62% of patients (182/293). Finally, one patient discontinued the TKI because of chemotherapy for another neoplasia. Reason of discontinuation was unknown 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 discontinuation, 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 TKIs. One-hundred sixty-two patients (55%) discontinued in first line, 117 patients (40%) in second line, 13 patients (4.5%) in third line, and 1 patient in fourth line. Among those who discontinued imatinib, 73 patients (35%) had been pre-treated with alpha-interferon (IFN) and 7 patients had been submitted to allogeneic stem cell transplantation. Median duration of treatment with any TKIs 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 TKIs 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 TKIs 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 TKIs patients (p<0.001). Overall, all patients but one had an optimal early response to last treatment: at 3 months of last TKI 34% of patients were in

MMR, 40% were in CCyR and/or had a transcript ≤ 1%, and 25% were in PCyR and/or had a transcript ≤ 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 TKIs (p=0.315).

Relapses and TFR

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 TKIs patients (Figure 1C).

The 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 TKIs 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 TKIs patients (at 26 months, Figure 1). There was no significant difference in TFR between patients who had discontinued imatinib first-line vs imatinib after IFN vs further lines (p=0.35), and there was no difference in TFR between patients who discontinued second generation TKIs frontline (n=33) vs second-line for intolerance (n=30) vs second-line for resistance (n=16) (p=0.16).

Overall 114 patients (39%) resumed treatment. Reasons for resuming were: loss of MR4 for 19% of patients, loss of MMR for 70% of patients, loss of CCyR for 9% of patients, other reasons for 2% of patients. There were no differences in reasons for restarting treatment between imatinib and second generation TKIs (p=0.13). Overall median time to restart treatment was 6 months (IQR 4-11). Although 75% of patients restarted treatment by the first year, last treatment resumption happened after 105 months of TFR. Median time to loss of MR4 was 3 months (IQR 2-7); median time to loss of MMR was 4 months (IQR 3-7); median time to loss of CCyR was 5 months (IQR 4-6). Median time from loss of response to restart-treatment was 1 month (IQR 0-2).

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 TKIs mainly stayed with second generation TKIs. Ninety-four percent of the patients who were retreated

achieved again at least a MMR and 82% of them achieved again a DMR fitting the criteria for a second discontinuation attempt.[31]

In 20 patients who had lost MR4 and in 4 patients who had lost MMR, the treatment was not resumed for a decision shared 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

We assessed in a univariate analysis age (considered as continuous variable), sex (female vs male), Sokal score (intermediate vs low; high vs low), type of therapy (2^{nd} generation TKIs vs imatinib), line of therapy at stop (imatinib vs imatinib post IFN; first line 2^{nd} generation vs 2^{nd} generation in second or further lines), type of transcript (b2a2 vs others), duration of therapy with the last TKI and any TKIs (continuous variables), duration of total treatment (continuous 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 statistical 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 TKIs in front line vs second line we observed that patients who discontinued treatment front-line had a significant 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 2^{nd} generations TKIs showed a better TFR (HR 0.43; IC 95% 0.20-0.91; Table 5, Figure 2). Duration of total treatment was positively associated with TFR among patients treated with 2^{nd} generation TKIs with a 22% risk reduction for 1 additional year of treatment (HR: 0.78; 95%CI 0.65-0.93).

Discussion

Although at present no guidelines expressively recommend treatment discontinuation, this study showed that many physicians have already experienced TKIs 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 prior 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 6 months, every 6 weeks for the subsequent 6 months and then every three months.[21] Although we may think that a stringent monitoring is protective, and indeed most of relapses occurred during the first year, late relapses were not complicated by loss of complete haematologic remission or progression to advanced phases even if monitoring was less frequent.[32] On this purpose it is mandatory to 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. While the history of CML was revolutionized by the introduction of imatinib that resulted in an extraordinary improvement of survival, 2nd generation TKIs 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, a definitive treatment discontinuation at present 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 like in the STIM and the Korean study.[7,16] Alike the ISAV trial,[13] 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 that can 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 TKIs in second line was significantly longer compared to patients who discontinued TKIs in front-line (128 vs 82 months). This could possibly account for the lower risk of relapses in patients who discontinued TKIs 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 2nd generation TKIs: we observed a 22% reduction of the risk of resuming therapy per year of treatment.

In this study we observed that patients who discontinued 2nd generation TKIs had a median duration of treatment with the last TKI of 50 months vs 96 months of treatment with imatinib (Table 1). The results are aligned with those of several prospective studies like the ENEST

Freedom, the ENEStop (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 2nd generation TKIs, with an estimated 57% relative risk reduction in favor of the 2nd generation TKIs. Even considering the quite large confidence interval, the minimum risk reduction is still 9%. These data are in keeping with the superiority of 2nd generation TKIs 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] As a matter of fact, Legros et al reported that 35% of patients, who had a second discontinuation attempt, after a median total time of treatment of 103 months, remained free from relapse at 3 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 in practice, confirming that treatment discontinuation is safe and effective also outside controlled clinical trials. Taking into account all the evidences collected in the last 10 years, we think that TKIs 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]

Authors Contributions: CF designed, performed the research, collected and analyzed the data and wrote the paper; GiSa, GR-C and MiBa designed the research and wrote the paper; ID and MaCe contributed to the management of the project and the collection of the data and reviewed the paper; PB analyzed the data, made the tables and reviewed the paper; MD, GR, FaCa, GG, BM, CG-P, EA, CE, PP, AG, IC, MiBe, MoCr, MoBo, SG, DR, AI, DC, RL, MaBe, MiCe, MS, MA, LuLe, FaSt, FrCa, NS, VG, LuLu, SR, PM, GC, FeSo, FI, FL, GiSp, FP and DF approved the project, contributed with the patient enrollment and reviewed the paper.

Conflict of interest disclosure: CF, GR-C, GR, FaCa, EA, PP, RL, MaBr, LuLe, FaSt, PM, FP and GiSa report honoraria from Novartis, Incyte, Bristol-Myers-Squibb (BMS) and Pfizer outside the

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All the other authors declare no competing interests.

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	Imatinib	2nd gen 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
1st line	129 (61)	33 (40)	162 (55)	
2nd line	81 (38.5)	36 (44)	117 (40)	
3rd line	1 (0.5)	12 (15)	13 (4.5)	
4th 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)	
ISAV[13]	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 TKIs (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

Table 1. Baseline patients' characteristics.

TKI: Tyrosine Kinase Inhibitor; MR: Molecular Response; DMR: Deep Molecular Response

	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	2 (2)	0 (0)	2 (2)

Table 2. Type of retreatment after failure of discontinuation.

	HR	95%CI		p-value
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				
2nd 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				
1st line vs ≥ 2nd 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 vs shared decision with MD	0.73	0.43	1.21	0.22

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

*For each variable the difference of months between groups of patients considered for computing HR corresponds to the IQR; ys: years; DMR: Deep Molecular Response; mos: months; MD: medical doctor

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

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

IQR: Interquartile Ranges

	HR	95%CI		p-value
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: 2nd vs 1st line	0.80	0.50	1.30	0.37
2nd generation TKIs vs imatinib	0.43	0.20	0.91	0.03
Duration of total therapy (1 yr increase) in patients treated with imatinib*	1.00	0.94	1.07	0.90
Duration of total therapy (1 yr increase) in patients treated with 2nd generation TKIs**	0.78	0.65	0.93	0.01

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

***** HR =1 expresses no risk increase associated to the increase of 1 year of the duration of therapy in patients treated with imatinib

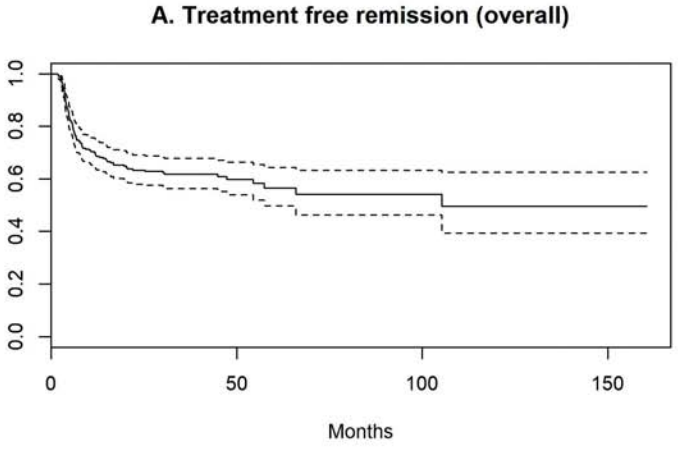
****** HR < 1 expresses the risk reduction associated to the increase of 1 year of the duration of therapy in patients treated with 2nd generation TKIs

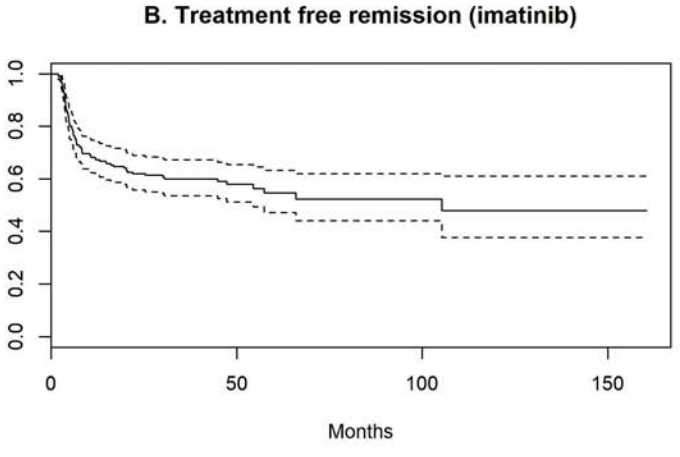
TKI: Tyrosine Kinase Inhibitor

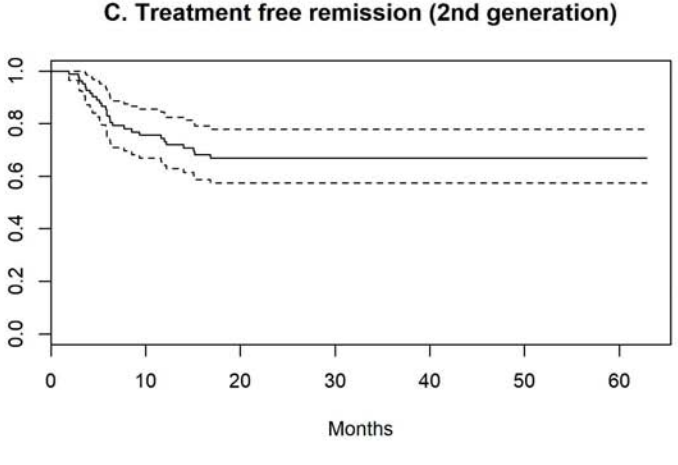
Figure 1. Kaplan-Meier curves for Italian patients who discontinued Tyrosine Kinase Inhibitors. Panel **A** represents the overall population; panel **B** represents patients who discontinued imatinib; panel **C** represents patients who discontinued 2nd generation Tyrosine Kinase Inhibitors. Estimated Treatment Free Remission is reported at 12 months for the overall population; at 12, 26 (median follow-up for patients who discontinued 2nd generation Tyrosine Kinase Inhibitors) and 42 months (median follow-up for patients who discontinued imatinib) for imatinib; at 12 and 26 months (median follow-up for patients who discontinued 2nd generation Tyrosine Kinase Inhibitors) for 2nd generation Tyrosine Kinase Inhibitors.

Figure 2. TKI-TFR curves adjusted for age at discontinuation, Sokal score, line of therapy and duration of disease.

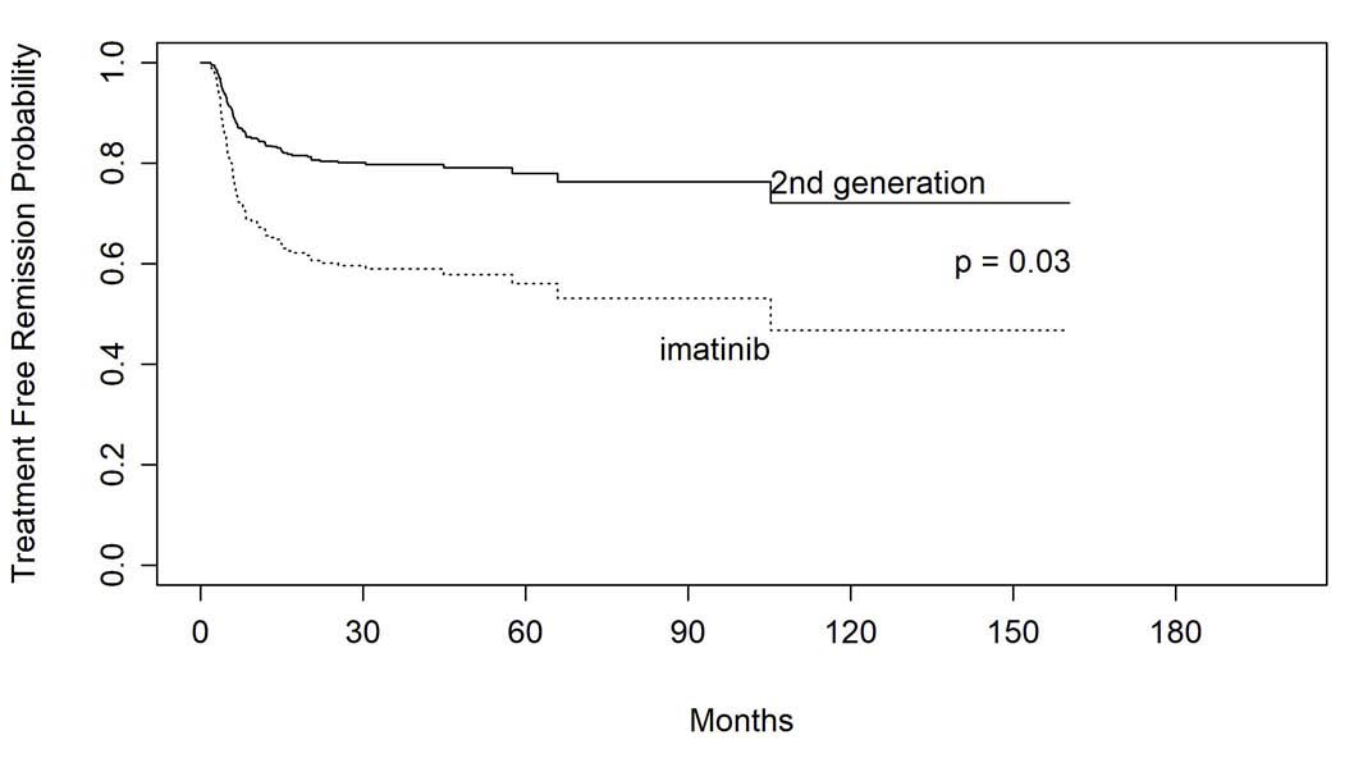
TKI: Tyrosine kinase Inhibitor; TFR: Treatment Free remission

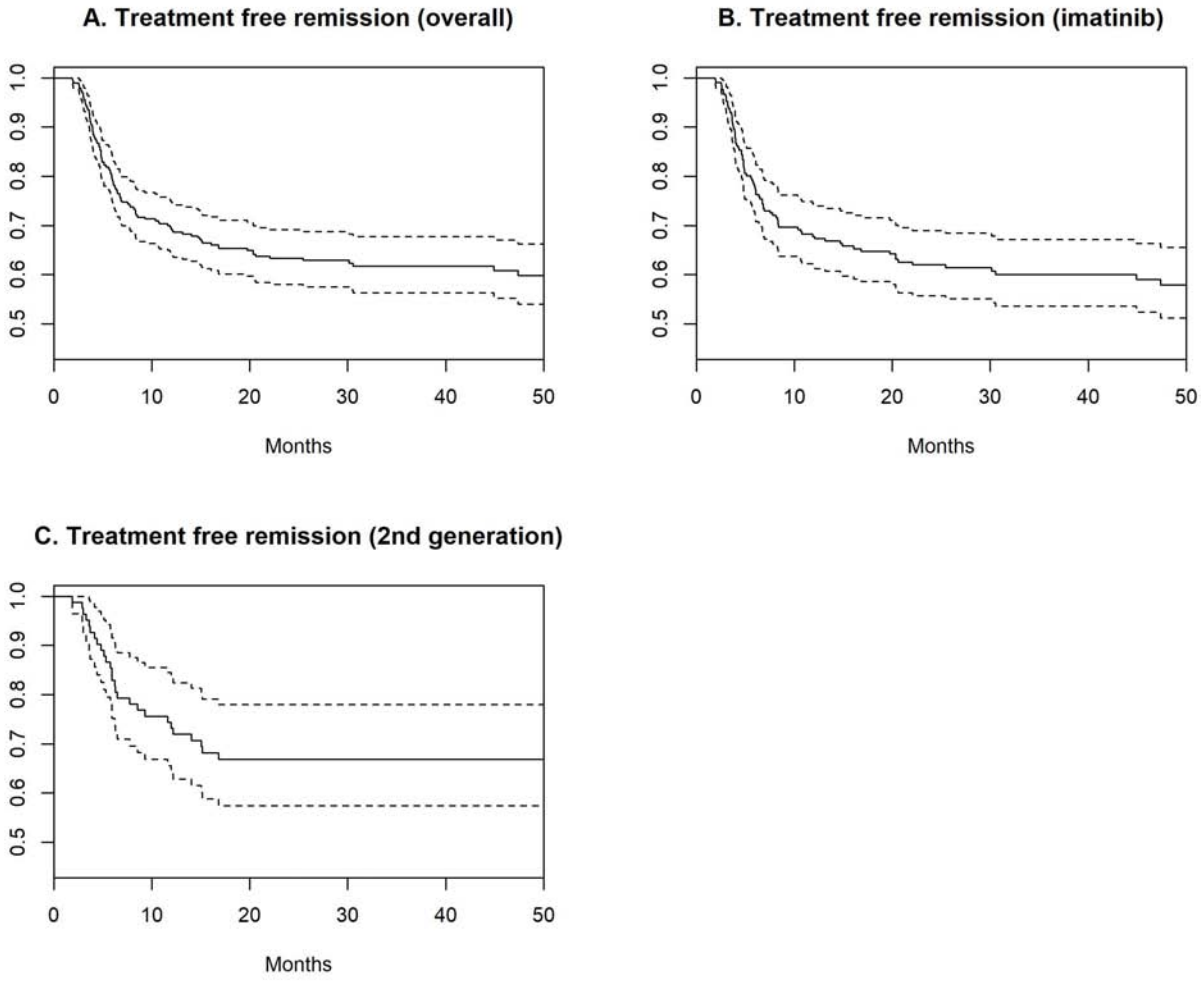






	Time	No at risk	No of events	TFR	CI95%	
Overall	12	203	90	69.30%	64.20%	74.80%
Imatinib	12	143	68	67.80%	61.80%	74.40%
	26	102	12	61.40%	55.10%	68.40%
	42	66	2	60.00%	53.60%	67.20%
2nd generation	12	60	22	73.20%	64.20%	83.40%
	26	32	5	66.90%	57.40%	77.90%


Treatment Free Remission Probability
0.0
0.2
0.4
0.6
0.8
1.0
2nd generation
p = 0.03
imatinib
0
30
60
90
120
150
180
Months



Suppl. 1. Pattern of the frequency of relapses over the first 50 months after treatment discontinuation. A) Kaplan-Meier curves for the overall population; B) Kaplan-Meier curves for patients who discontinued imatinib; C) Kaplan-Meier curves for patients who discontinued 2nd generation Tyrosine Kinase Inhibitors.