Feasibility of Treatment Discontinuation in Chronic Myeloid Leukemia in Clinical Practice in Spain: Results from a Nationwide Series of 236 Patients.

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Abstract

Introduction: Over half of patients with chronic myeloid leukemia (CML) in sustained deep molecular remission do not lose the major molecular response (MMR) after stopping treatment with tyrosine kinase inhibitors (TKI). This strategy is safe in controlled clinical trials, but there is scarce information on its applicability in the real-life setting. We aimed to assess if treatment cessation was feasible in clinical practice in a large nationwide series of CML patients from Spain.

Methods: This retrospective study comprised a series of 236 patients in chronic-phase CML who discontinued TKI treatment outside of clinical trials between April 2009 and February 2018 in 33 Spanish institutions. Inclusion criteria were: a) TKI treatment duration >3 years; b) sustained MR4.5 in >4 consecutive determinations (one single point in MR4 was acceptable) during >2 years; c) molecular monitoring in a reference laboratory expressing the results on the International Scale (IS). Patients who had undergone allogeneic hematopoietic stem-cell transplantation were excluded. Molecular relapse was defined as consecutively detectable BCR-ABL1 transcripts showing a ≥1 log increase or loss of MMR in any single sample. Treatment-free remission (TFR) was estimated by the method of Kaplan-Meier and defined as the time from TKI discontinuation to the date of restarting therapy for any reason or, if treatment was not restarted, the date of last contact. Incidence of molecular relapse was calculated using the cumulative incidence function with resumption of TKI treatment in the absence of molecular relapse and death in MMR as competing events. Analysis of factors predicting molecular relapse was done by the method of Fine and Gray.

Results: Table 1 shows the main characteristics of the series. Median follow-up from treatment discontinuation was 21.5 months, and 5 patients died in MMR due to CML unrelated causes. TKI therapy was reinitiated due to molecular relapse (MMR loss: n=52, increase >1 log in BCR-ABL transcript level at two consecutive assessments without losing MMR: n=12), patient preference (n=2), and severe withdrawal

syndrome (n=1). One additional patient lost MMR after 20 months from treatment cessation but decided not to be retreated, with spontaneous recovery of MMR. The probability of TFR at 4 years was 64% (95% Confidence Interval [CI]: 55%-72%)(Figure 1). The cumulative incidence of molecular recurrence was 33% (95% CI: 26%-38%) at 3 years (Figure 2). Forty-nine relapses (75% of total) occurred in the first 6 months. The latest MMR loss was detected 30 months after treatment stop. One patient restarted treatment 44 months after TKI discontinuation due to ≥1 log increase in BCR-ABL1 transcripts in two consecutive samples without losing MMR. In univariate analysis, duration of TKI treatment of less than 5 years (P=0.005) and time in RM4.5 shorter than 4 years before TKI discontinuation (P=0.003) were both significantly associated with a higher incidence of molecular recurrence.

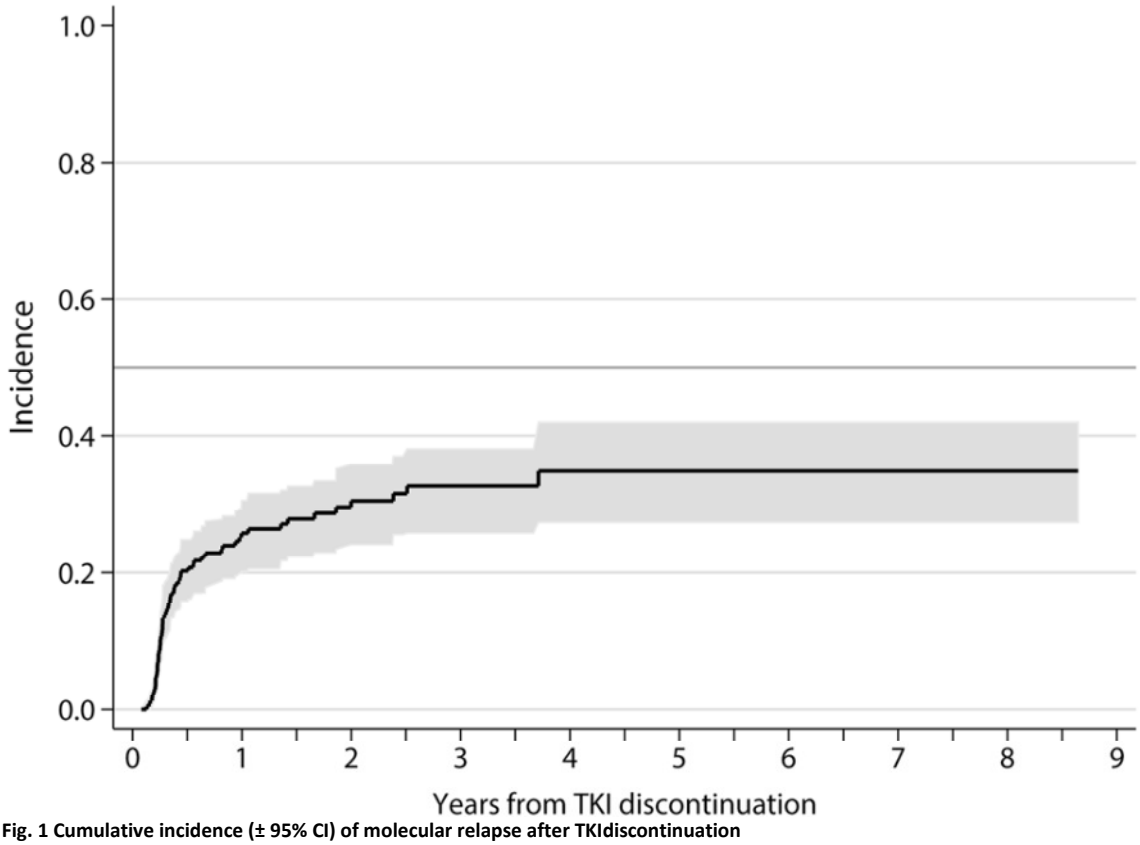

Fig. 1 Cumulative incidence (± 95% CI) of molecular relapse after TKIdiscontinuation

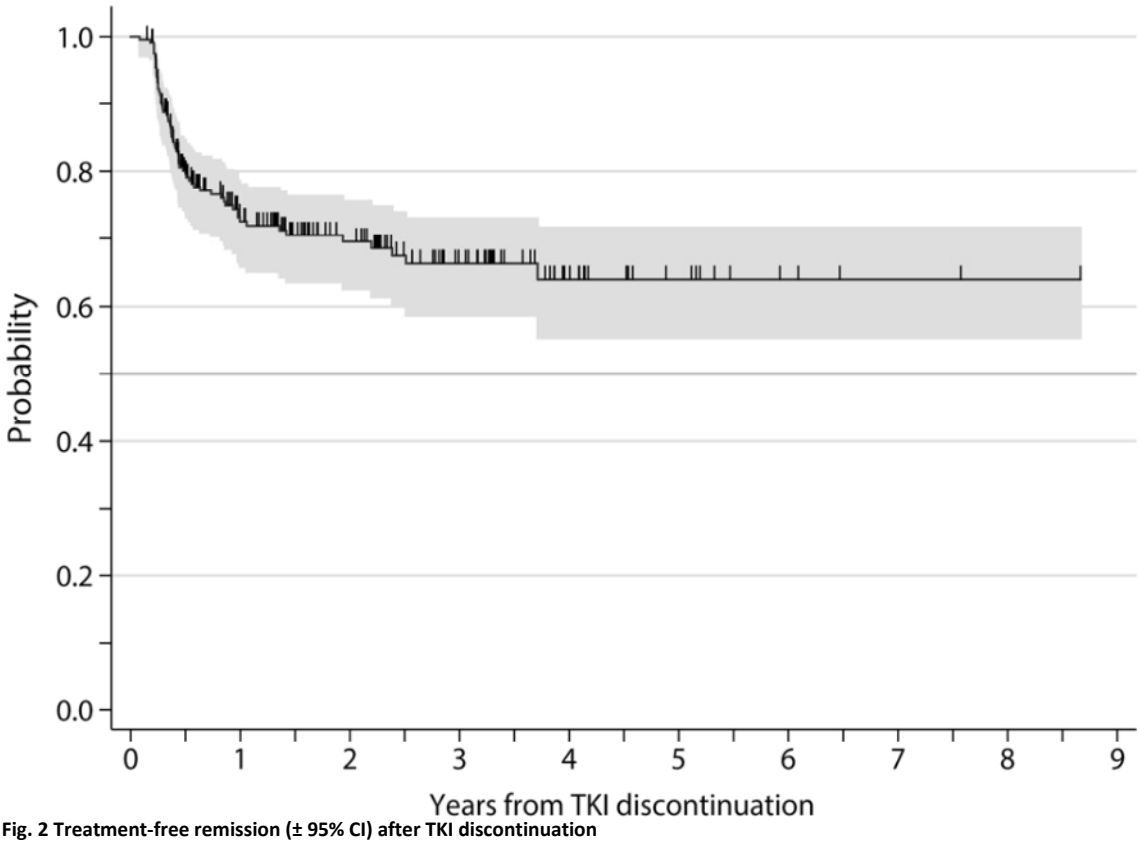

Fig. 2 Treatment-free remission (± 95% CI) after TKI discontinuation

No patient progressed to the advanced phases of CML. At the time of restarting treatment, the median BCR-ABL1 IS was 0.3%, with this value being >5% in only 7 instances. Most patients (81%) received the same TKI that they were taking before the trial of treatment cessation. Median follow-up after treatment resumption was 20 months. Among the 64 patients who restarted treatment due to molecular relapse, 46 of 52 cases regained MMR after a median time of 3 months, and 47 of 64 regained MR4.5 after a median time of 5 months. Response status at last control was: MR4.5 (n=196), MR4 (n=15), MMR (n=14), complete cytogenetic response (n=10), and other (n=1).

Fifty-one patients (22%) developed musculoskeletal or joint pain after treatment cessation. In patients stopping imatinib, a significant increase in Hb levels, leukocyte counts, total lymphocyte counts, platelet counts, and cholesterol levels was observed. At 6 months, an increase in Hb level >2 g/dL was observed in 47% of patients with anemia. By contrast, nilotinib discontinuation was not followed by any relevant change in laboratory values.

Conclusions: Our results confirm that treatment discontinuation is feasible and safe in clinical practice in Spain. Duration of TKI treatment of less than 5 years and a time in RM4.5 shorter than 4 years before TKI discontinuation were significantly associated with a higher incidence of molecular recurrence.

Table 1 Demographics and treatment history of 236 chronic-phase CML patients who discontinued TKI treatment in DMR in Spain from April 2009 to February 2018.

Age at diagnosis, year[a]	50 (40–61)
Age at TKI discontinuation, year[a]	61 (52–72)
Sex, females (%)	123 (52)
Sokal risk score, n (%)	
Low	129 (60)
Intermediate	69 (32)
High	17 (8)
Unknown	21
Time from diagnosis to TKI discontinuation, monthsa	130 (96–162)
Prior interferon treatment, n (%)	55 (23)
TKI lines before TKI discontinuation, n (%)	
One	184 (78)
Two	32 (14)
Three	20 (8)
TKI at the time of treatment cessation, n (%)	
Imatinib	175 (74)
Nilotinib	41 (17.5)
Dasatinib	17 (7)
Bosutinib	1 (0.5)
Ponatinib	2 (1)
History of resistance to any TKI, n (%)	17 (7)
Duration of TKI treatment, monthsa	123.5 (93–150)
Time in MR4.5 before TKI discontinuation, monthsa	68 (40–100)

DMR deep molecular response, TKI tyrosine kinase inhibitor
[a]Median (interquartile range)

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Topics: leukemia, myelocytic, chronic, spain, withdrawing treatment, protein-tyrosine kinase inhibitor, measles-mumps-rubella vaccine, withholding treatment, disease remission, follow-up, anemia, arthralgia

Author notes: *Asterisk with author names denotes non-ASH members.