CML AdvocatesNetwork

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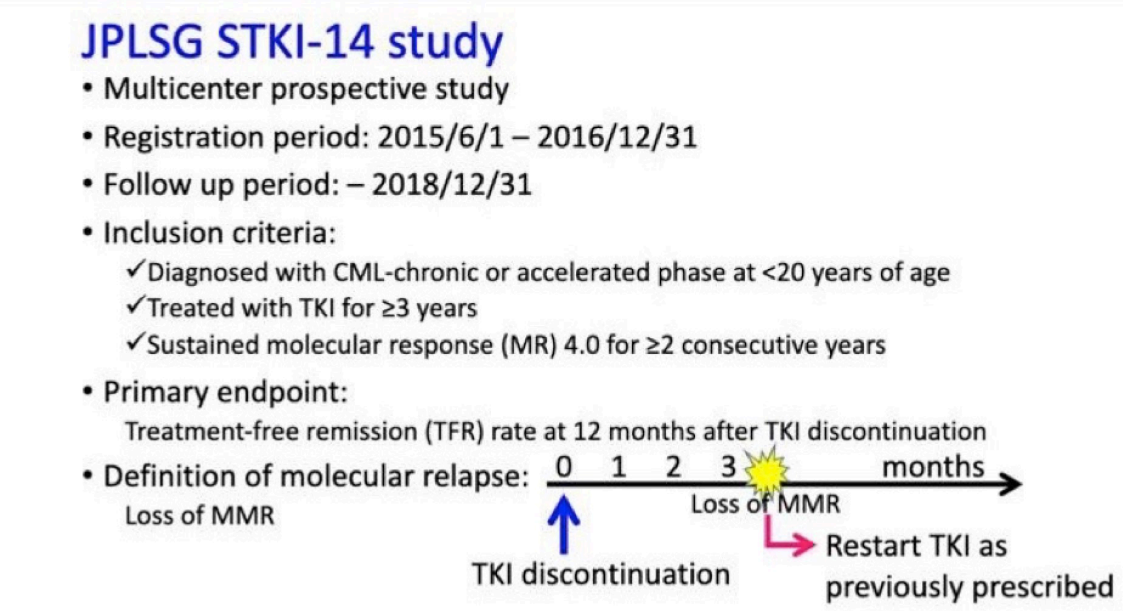
Results from ASH: Discontinuation of TKIs in children with CML (JPLSG STKI-14 study)

TKIs seem to allow most CML patients, including children, to live a normal lifespan under continued treatment. However, the medication's long-term side effects such as growth impairment and the need to take the drug for the rest of life, are an issue of concern especially for children.

Recent clinical trials in adults have suggested that some CML patients in deep molecular response on TKI therapy may have chance to discontinue TKI treatment. However, the biology of CML in children may differ from adults with more aggressive presentation, and data of TKI discontinuation in CML children are limited.



In 2015-2016, the Japan Pediatric Leukemia/Lymphoma Study Group (JPLSG) recruited 22 Japanese patients diagnosed with CML in chronic phase at less than 20 years of age, treated with TKI for at least 3 years, and in sustained molecular response (MR4) for at least 2 preceding years.

Patients who relapsed after hematopoietic stem cell transplantation (HSCT) were included if total duration of TKI treatment was at least 3 years after rejection and relapse, and also met the criteria mentioned above.

The study group prospectively analyzed treatment-free remission rate (TFR) at 12 months. Treatment was restarted in molecular relapse which was defined as at least one loss of major molecular response (MMR- PCR above 0.1 %).

Patients characteristics — n (%), or median (IQR)

		n=22
Age at diagnosis, years		9 (3 – 11)
Age at TKI discontinuation, years		16 (15 – 18)
Sex		Male 16 (72)/Female 6 (28)
Sokal score; low/intermediate/high		17/3/2 (77/14/9)
EUTOS score; low/high		18/4 (82/18)
Interferon alpha before TKI		2 (9)
Type of TKI	Imatinib only	19 (86)
	2nd generation TKI +/- imatinib	3 (14)
Prior HSCT		3 (14)
Duration of TKI before TKI discontinuation, months		102 (63 – 136)
Duration of MR4.0 before TKI discontinuation, months		53.5 (40 –78)
Time of TKI treatment before MR4.0, months		22 (15 – 36)

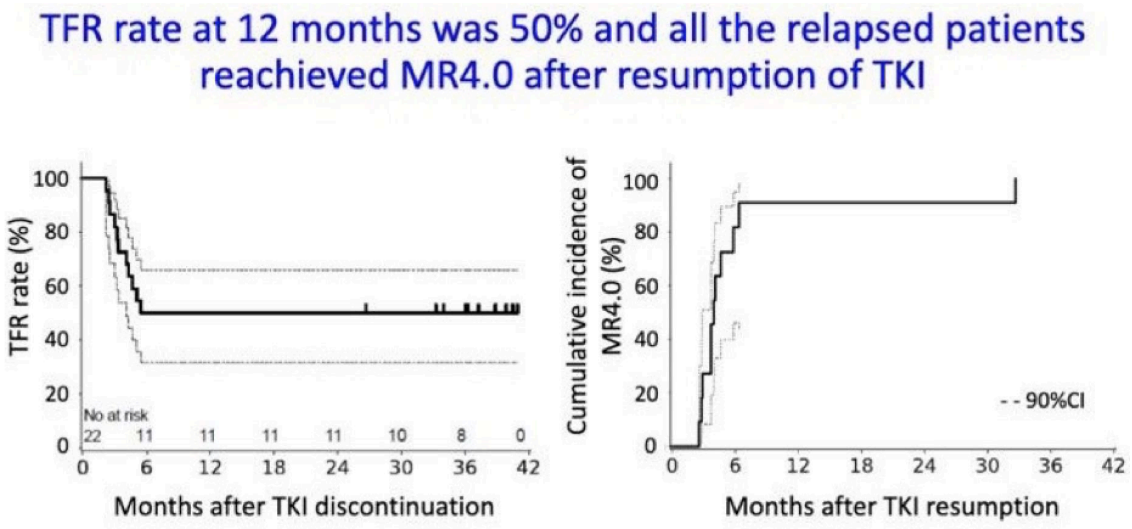
All patients were diagnosed with CML in chronic phase. Median age at diagnosis of CML was 9 years (range, 3-11 years), and median age at discontinuation of TKI was 16 years (range, 15-18 years).

Initial TKI was imatinib in 21 patients, and imatinib was switched to second generation TKI in 2 patients because of intolerance or poor response. One patient was treated only with 2G-TKI. Median treatment duration of TKI before discontinuation was 102 months (range, 63-136 months), and median duration of MR4.0 was 22 months (range, 15-36 months).

Half of the patients remained in therapy-free remission at 12 months and TFR rate was 50.0%. The other patients experienced molecular relapse and restarted TKI at median of 102 days (range, 67 to166 days) after discontinuation of TKI. No progression was observed during study, and all 11 patients who relapsed reachieved MR 4.0 at median of 64 days (range, 25 to 196 days) after restart of TKI.

All the patients who lost MR 4.0 within 3 months after stopping TKI failed to maintain MMR thereafter and restarted TKI. On the other hand, a single patient who lost MR4.0 after 32 months of stopping TKI reachieved MR 4.0 again without TKI.

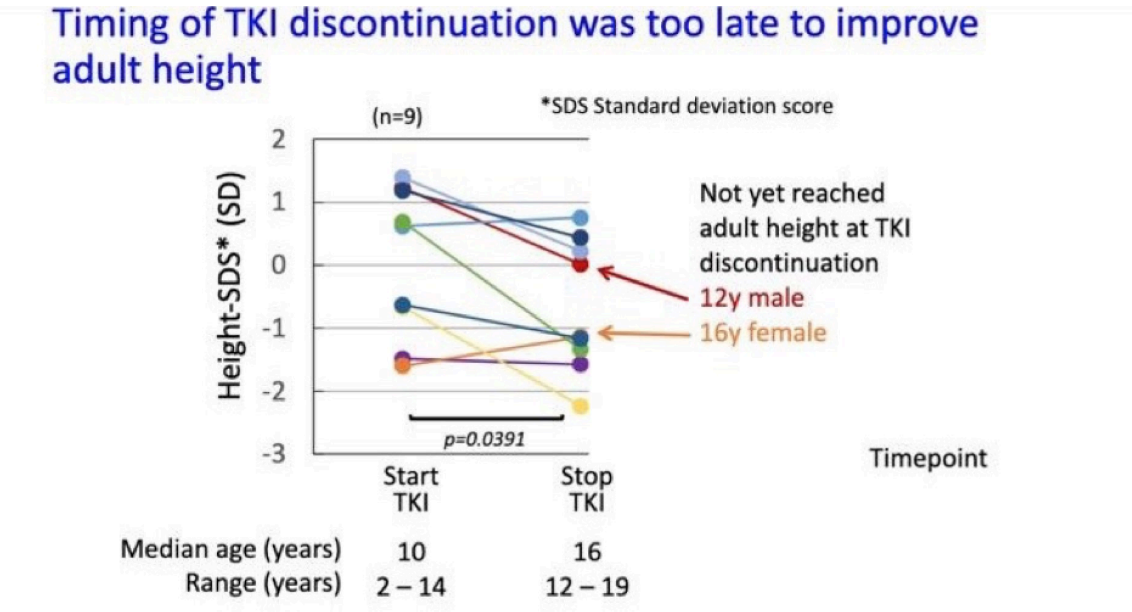
Plasma trough concentration level of imatinib was determined just before stopping imatinib in 18 patients. In univariate analysis, plasma concentration level of imatinib was associated with successful TFR after stopping TKI (p=0·005). Higher plasma concentration of imatinib was associated with higher risk of relapse. In contrast, treatment duration of TKI, duration of MR4.0, Sokal, Hasford, or EUTOS scores had no impact on TFR.



Of 3 patients who underwent HSCT, 2 patients succeeded in maintenance of MR4.0 without TKI. In terms of adverse effects, grade 1 musculoskeletal or joint pain observed in 3 patients, and grade 1 to 3 elevation of creatine phosphokinase observed in 6 patients regressed after discontinuation of TKI. No withdrawal symptoms as reported in adults was observed in this study.

In 3 males who discontinued TKI before puberty (5, 9, and 13 years of age with testicular size < 3mL), slight recovery in growth associated with increase in both serum bone type alkaline phosphatase and urine N-Telopeptides of Type I collagen was observed soon after discontinuation of TKI.

However, these 3 patients relapsed and restarted TKI within 4 months after discontinuation of TKI. In general, timing of TKI discontinuation of these patients seemed to be too late to achieve standard adult height after discontinuation.



Conclusion: The rate of therapy-free remission rates in children was comparable to that observed in STOP studies with adults. The data indicates that TKI may be safely discontinued also in children younger than 15 years of age at diagnosis, treated with TKI for ≥ 3 years, and sustained MR4.0 for ≥ 2 years, including patients who relapsed after HSCT.

All patients who had to restart treatment re-achieved deep molecular response after restarting treatment. No withdrawal symptoms were observed in those children.

However, the timing of TKI discontinuation was too late to achieve adult body height in this study. Further studies of TKI discontinuation in children with CML are expected.