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Durable remission after treatment with very low doses of imatinib for FIP1L1-PDGFR α -positive chronic eosinophilic leukaemia

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To the Editor

The exquisite response to imatinib mesylate in patients with chronic eosinophilic leukaemia (CEL) harbouring the FIP1L1-PDGFR α (F/P) fusion transcript has been well documented [1,2,3,4]. In the up-to-date largest multicentre study, all 27 patients with detectable F/P mutation achieved complete haematological and molecular remission after imatinib therapy and have remained in continuous remission after median of 25 months [2].

The initial daily doses of imatinib ranged from 100 to 400mg in a majority of published reports, but maintained imatinib doses were not fully established [2,5]. It was also demonstrated that imatinib dose reduction or temporary discontinuation were associated with molecular and clinical relapse [6,7]. Additionally, single cases of imatinib-resistant F/P-positive CEL have been reported [8].

As the response rate after imatinib is close to 100%, the current issue is 1) to establish a minimal effective imatinib dose needed to remission maintenance and 2) to evaluate the duration of imatinib response.

Recently, we reported on high efficacy of weekly imatinib schedule in 13 F/P-positive CEL patients. Imatinib at weekly dosage seemed to be sufficient to maintain haematological and molecular remission with a median of 21 months of follow-up in this studied subgroup [9].

Herein we present long-term results of F/P-positive CEL after imatinib. The data were collected from ten centres in Poland. All patients gave written informed consent. Twenty male and two female patients at median age of 52 years (range 22-80 years) were included in this **partially retrospective** study. Organ involvement was demonstrated in 91% of patients and splenomegaly was the most common clinical manifestation. 23% of patients were asymptomatic at diagnosis. Median blood eosinophilia and median bone marrow eosinophil infiltration were $12 \times 10^9/L$ (range 2.5-40) and 39.5% (range 7.0-80), respectively. The starting, de-escalated and maintained imatinib doses were left to the physician's discretion. The initial imatinib doses were as follows: 100mg/day (n=18), 400mg/day (n=3) and 300mg/day (n=1). All treated patients achieved haematological remission after median of 13 days (range 3-90). Complete molecular remission by nested RT-PCR was confirmed after median of 10 months (range 3-24). They became free of symptoms. The maintained imatinib doses were following: 100mg per week (n=11), 200mg per week (n=2), 400mg per week (n=1), 100mg twice a week (n=2), 100mg thrice a week (n=2) and 100mg a day (n=4). Imatinib doses and duration of treatment were shown in table 1. All studied patients remained in complete haematological and molecular remission after median follow-up of 41 months (range 11-71). Median time at maintained imatinib doses was 27 months (range 2-61). Imatinib plasma levels were measured using High-Performance Liquid Chromatography-Tandem Mass Spectrometry method [10]. Blood samples were taken 24 hours after the last imatinib intake from eleven patients; from 9 patients on 100mg weekly imatinib and from 2 on imatinib at 200mg a week. Imatinib plasma levels appeared to be extremely low and ranged between 44-164 ng/ml and 103-203 ng/ml, respectively for both analyzed groups. Of note is, that F/P negativity was confirmed at the same time points by nested RT-PCR.

With this large series of F/P-positive CEL patients we can confirm that imatinib may induce durable remission with the maximum follow-up of 71 months until last contact. Most recently, Rondoni *et al.* [11] presented the follow-up results of 33 F/P-positive CEL patients on imatinib with a continuous remission after median of 51 months (range 30-92). In contrary to our report, the maintained imatinib doses were 100mg a day. It is noteworthy that 18 patients from our study group received imatinib at total maintained doses of 400mg a week or less. We have proved that treatment with such low imatinib doses may maintain molecular remission despite low imatinib plasma levels. **Nevertheless the longer follow-up is needed to confirm our encouraging results.**

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Table 1. Imatinib doses and duration of therapy in F/P-positive CEL patients

patients	Starting imatinib dose (mg/day)	first de-escalated imatinib dose (mg)	maintained imatinib dose (mg)	plasma imatinib level at maintained imatinib dose (ng/ml)	months on maintained imatinib dose	Total time on imatinib (months)
Patient 1.	100	200 per week	100 per week	46	54	67
Patient 2.	100	200 per week	100 per week	47	61	66
Patient 3.	400	400 per week	100 per week	44	3	12
Patient 4	100	100 BIW	100 per week	125	18	54
Patient 5.	100	100 per week	100 per week	24	34	37
Patient 6.	100	100 per week	100 per week	67	31	40
Patient 7.	100	100 per week	100 per week	99	29	30
Patient 8.	100	100 per week	100 per week	164	56	58
Patient 9.	100	100 BIW	100 per week	123	8	17
Patient 10.	100	100 per week	100 per week	ND	15	51
Patient 11.	100	100 per week	100 per week	ND	16	19
Patient 12.	400	100 daily	200 per week	ND	41	63
Patient 13.	400	100 daily	200 per week	ND	43	45
Patient 14.	100	100 BIW	100 BIW	103	27	28
Patient 15.	100	100 BIW	100 BIW	203	4	14
Patient 16.	100	100 TIW	100 TIW	ND	16	64
Patient 17.	100	100 TIW	100 TIW	ND	11	71
Patient 18.	100	100 BIW	400 per week	ND	2	39
Patient 19.	100	NA	100 daily	ND	NA	50
Patient 20.	100	NA	100 daily	ND	NA	37
Patient 21	100	NA	100 daily	ND	NA	11
Patient 22	300	100 daily	100 daily	ND	40	41

Legend: BIW-twice a week, TIW-thrice a week, ND-not done, NA-not applicable