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LETTER TO THE EDITOR

Durable remission after treatment with very low doses of imatinib for FIP1L1-PDGFRα-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-PDGFRα (F/P) fusion transcript has been well documented [1–4]. 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 400 mg 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 was 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. At diagnosis, 23% of patients were asymptomatic. Median blood

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eosinophilia and median bone marrow eosinophil infiltration were 12×10^9/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: 100 mg/day ($n = 18$), 400 mg/day ($n = 3$) and 300 mg/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: 100 mg per week ($n = 11$), 200 mg per week ($n = 2$), 400 mg per week ($n = 1$), 100 mg twice a week ($n = 2$), 100 mg thrice a week ($n = 2$) and 100 mg 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 h after the last imatinib intake from eleven patients: from 9 patients on 100 mg weekly imatinib and from 2 on imatinib at 200 mg a week. Imatinib plasma levels appeared to be extremely low and ranged between 44 and 164 ng/ml and 103–203 ng/ml, respectively, for both analysed 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 100 mg a day. It is noteworthy that 18 patients from our study group received imatinib at total maintained doses of 400 mg 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.

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

BIW twice a week, *TIW* thrice a week, *ND* not done, *NA* not applicable

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