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

Grzegorz Helbig, Andrzej Moskwa, Marek Hus, Jarosław Piszcz, Alina Swiderska, Alina Urbanowicz, Małgorzata Całbecka, Ilona Seferyńska, Małgorzata Raźny, Marek Rodzaj, Ewa Żuk, Sławomira Kyrcz-Krzemień

1. Departament of Haematology and Bone Marrow Transplantation, Silesian Medical University, Katowice, Poland.
2. Department of Haematology, Provincial Hospital, Gorzow, Poland.
3. Department of Haematology, Medical University, Lublin, Poland.
4. Department of Haematology, Medical University, Białystok, Poland.
5. Department of Haematology, Provincial Hospital, Zielona Góra, Poland.
6. Department of Haematology, Provincial Hospital, Suwałki, Poland
7. Department of Haematology, Provincial Hospital, Toruń, Poland
8. Institute of Haematology and Transfusion Medicine, Medical University, Warsaw, Poland
9. Department of Haematology and Internal Medicine, Rydygier Hospital, Kraków, Poland
10. Department of Haematology, Provincial Hospital, Szczecin, Poland

Corresponding author: Grzegorz Helbig MD, PhD, Department of Haematology and Bone Marrow Transplantation, Silesian Medical University, Katowice, Poland. Phone: 0048322591310, fax 0048322554985, e-mail: ghelbig@o2.pl

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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 [1,2,3,4]. 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 12x10^9/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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| 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 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                        | 99                         |                                                          | 29                               | 30                             |
| Patient 8. | 100                           | 100 per week                        | 100 per week               | 164                                                      | 56                               | 58                             |
| Patient 9. | 100 BIW                       | 100 per week                        | ND                         | 123                                                      | 8                                | 17                             |
| Patient 10. | 100                           | 100 per week                        | ND                         |                                                          | 15                               | 51                             |
| Patient 11. | 100                           | 100 per week                        | ND                         |                                                          | 16                               | 19                             |
| Patient 12. | 400 daily                      | 200 per week                        | ND                         |                                                          | 41                               | 63                             |
| Patient 13. | 400                           | 100 daily                           | 200 per week               | ND                                                       | 43                               | 45                             |
| Patient 14. | 100 BIW                       | 100 BIW                             | 103                        |                                                          | 27                               | 28                             |
| Patient 15. | 100                           | 100 BIW                             | 203                        |                                                          | 4                                | 14                             |
| Patient 16. | 100 TIW                       | 100 TIW                             | ND                         |                                                          | 16                               | 64                             |
| Patient 17. | 100 TIW                       | 100 TIW                             | ND                         |                                                          | 11                               | 71                             |
| Patient 18. | 100                           | 100 BIW                             | 100 BIW                    | ND                                                      | 2                                | 39                             |
| Patient 19. | 100 NA daily                   | 100 daily                           | ND                         |                                                          | NA                               | 50                             |
| Patient 20. | 100 NA daily                   | 100 daily                           | ND                         |                                                          | NA                               | 37                             |
| Patient 21. | 100 NA daily                   | 100 daily                           | ND                         |                                                          | NA                               | 11                             |
| Patient 22. | 300                           | 100 daily                           | ND                         |                                                          | 40                               | 41                             |

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