



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

Grzegorz Helbig, Andrzej Moskwa, Marek Hus, Jaroslaw Piszcz, Alina Swiderska, Alina Urbanowicz, Malgorzata Calbecka, Ilona Seferyńska, Malgorzata Rażny, Marek Rodzaj, et al.

► To cite this version:

Grzegorz Helbig, Andrzej Moskwa, Marek Hus, Jaroslaw Piszcz, Alina Swiderska, et al.. Durable remission after treatment with very low doses of imatinib for FIP1L1-PDGFR α -positive chronic eosinophilic leukaemia. *Cancer Chemotherapy and Pharmacology*, 2011, 67 (4), pp.967-969. 10.1007/s00280-011-1582-3 . hal-00671228

HAL Id: hal-00671228

<https://hal.science/hal-00671228>

Submitted on 17 Feb 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Grzegorz Helbig,¹ Andrzej Moskwa,² Marek Hus,³ Jarosław Piszcz,⁴ Alina Swiderska,⁵ Alina Urbanowicz,⁶ Małgorzata Całbecka,⁷ Ilona Seferyńska,⁸ Małgorzata Rażny,⁹ Marek Rodzaj,⁹ Ewa Żuk,¹⁰ Sławomira Kyrzcz-Krzemień¹

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

Key words: chronic eosinophilic leukaemia, imatinib, FIP1L1-PDGFR α

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.**

References

1. Cools J, De Angelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J et al (2003) A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med.* 348; 1201-1214.
2. Baccarani M, Cilloni D, Rondoni M, Ottaviani E, Messa F, Merante S et al (2007) The efficacy of imatinib mesylate in patients with FIP1L1-PDGFR α positive hypereosinophilic syndrome. Results of a multicenter prospective study. *Haematologica.* 92; 1173-1179.
3. Helbig G, Stella-Holowiecka B, Grosicki S, Bober G, Krawczyk M, Wojnar J et al. (2006) The results of imatinib therapy for patients with primary eosinophilic disorders. *Eur J Haematol.* 76; 535-536.
4. Vandenberghe P, Wlodarska I, Michaux L, Zachee P, Boogaerts M, Vanstraelen D et al. (2004) Clinical and molecular features of FIP1L1-PDGFR α (+) chronic eosinophilic leukemia. *Leukemia.* 18; 734-742.
5. Metzgeroth G, Walz C, Erben P, Popp H, Schmitt-Graeff A, Haferlach C et al. (2008) Safety and efficacy of imatinib in chronic eosinophilic leukaemia and hypereosinophilic syndrome-a phase-II study. *Brit J Haematol.* 143; 707-715.
6. Klion AD, Robyn J, Maric I, Fu W, Schmid L, Lemery S et al (2007) Relapse following discontinuation of imatinib mesylate therapy for FIP1L1/PDGFR α -positive chronic eosinophilic leukemia: implications for optimal dosing. *Blood.* 110; 3552-3556.
7. Jovanovic J, Score J, Waghorn K, Cilloni D, Gottardi E, Metzgeroth G et al (2007) Low-dose imatinib mesylate leads to rapid induction of major molecular response and achievement of complete molecular remission in FIP1L1-PDGFR α positive chronic eosinophilic leukemia. *Blood.* 109; 4635-4641.
8. Lierman E, Michaux L, Beullens E, Pierre P, Marynen P, Cools J et al (2009) FIP1L1-PDGFR α D842V, a novel panresistant mutant, emerging after treatment of FIP1L1-PDGF T674I eosinophilic leukaemia with single agent sorafenib. *Leukemia.* 23; 845-851.
9. Helbig G, Moskwa A, Świdarska A, Urbanowicz A, Całbecka M, Gajkowska J et al (2009) Weekly imatinib dosage for chronic eosinophilic leukaemia expressing FIP1L1-PDGFR α fusion transcript: extended follow-up. *Brit J Haematol.* 145: 132-134.
10. Titier K, Picard S, Ducint D, Teilhet E, Moore N, Berthaud P et al (2005) Quantification of imatinib in human plasma by high-performance liquid chromatography-tandem mass spectrometry. *Ther Drug Monit.* 27: 634-640.
11. Rondoni M, Ottaviani E, Cilloni D, Piccaluga P, Paolini S, Iacobucci I et al. (2009) Chronic eosinophilic leukemia with FIP1L1-PDGFR α rearrangement: the response to imatinib is durable. A report of 33 patients with a follow-up of 30 to 92 months. *Blood* 114; 22 abstract 3894.

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