RESEARCH LETTER

Exquisite response to imatinib mesylate in *FIP1L1-PDGFRA*-mutated hypereosinophilic syndrome: a 12-year experience of the Polish Hypereosinophilic Syndrome Study Group

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Introduction Hypereosinophilic syndrome (HES) constitutes a heterogeneous group of disorders characterized by 1) peripheral blood eosinophilia with eosinophil count of 1.5×10^9/l or higher documented on at least 2 occasions or marked tissue eosinophilia, and 2) the occurrence of eosinophilia-related organ damage.[1] In 2003, a unique molecular finding known as the Fip1-like1 (*FIP1L1*)–platelet-derived growth factor receptor alpha (*PDGFRA*) (F/P) rearrangement was detected in approximately 10% to 20% of patients with HES.[2] As the result of widespread recognition of the growing number of molecular abnormalities in eosinophilia-related disorders, a new category within the 2008 World Health Organization classification was established: myeloid and lymphoid neoplasms with eosinophilia and rearrangements of *PDGFRA* (mainly F/P), *PDGFRB* and fibroblast growth factor receptor 1 (*FGFR1*).[3] The F/P rearrangement remains occult by conventional cytogenetics, but it can be detected with the use of reverse transcriptase–polymerase chain reaction or fluorescence in situ hybridization for the *CHIC2* deletion.[4]

It was demonstrated that the presence of F/P fusion gene is associated with the overexpression of an aberrant tyrosine kinase and shows an excellent sensitivity to tyrosine kinase inhibitor, imatinib mesylate (IM).[2]

For unknown reasons, the majority of patients with F/P rearrangement are male, usually between 20 and 40 years of age. Before the introduction of IM treatment, the prognosis of F/P-mutated HES was poor with a 5-year mortality of 30% to 50%, mainly due to the irreversible cardiac failure.[5]

Herein, we update our 12-year experience with IM treatment for F/P-mutated HES. Moreover, the outcome of patients who discontinued IM after achieving in-depth molecular response is also presented.

Patients and methods We evaluated the demographics, clinical and laboratory data as well as long-term results of patients with F/P mutation receiving IM treatment from six Polish institutions. The first patient was recruited in 2003 and the last initiated the treatment in 2017. The starting and maintenance doses of IM were left at the physician's discretion and depended on institution's policy; however, a weekly IM dose was established as an end-point. Patients in whom F/P-mutated HES was diagnosed before 2014 received branded IM (Glivec, Novartis, Basel, Switzerland) and were consequently switched to one of the generics available on the market. Those who were diagnosed after 2014 received generic IM from the very beginning of the therapy. Discontinuation of IM was recommended for patients who achieved durable (at least 2 years) in-depth molecular remission. Reverse transcriptase–polymerase chain reaction was used to detect the presence of the F/P fusion gene in peripheral blood or bone marrow samples.[2] The molecular assay was repeated every 3 to 6 months and then yearly.

TABLE 1 Large studies with imatinib mesylate for *FIP1L1-PDGFRA*–mutated hypereosinophilic syndrome

Patients, n	CHR rate, %	CMR rate, %	Median follow-up, y	References
16	95	87	1.8	Metzgeroth et al[7]
44	100	95	4.3	Legrand et al[8]
22	95	100	6	Pardanani et al[9]
33	94	97	5.1	Qu et al[10]
32	100	100	11.9[a]	This study

a n = 22

Abbreviations: CHR, complete hematological response; CMR, complete molecular response

Complete hematological response (CHR) was defined as normalization (<0.7×10^9/l) of peripheral blood eosinophilia with normal hemoglobin level and platelet count and resolution of end-organ damage (by ultrasound and/or computed tomography) if manifested before the commencement of IM therapy. Undetectable F/P rearrangement on polymerase chain reaction defined complete molecular response (CMR). Data updates on patients' outcome were requested from all centers and the results were provided for 22 patients. All patients provided an informed consent in accordance with the Declaration of Helsinki. Imatinib remained a standard treatment for F/P-mutated HES and the approval from ethics committee was not required.

Results A total of 32 patients (30 male and 2 female) meeting the HES criteria[1] and harboring the F/P transcript were included in this analysis. The median (range) age was 51 (19–80) years. At diagnosis, 14 (44%) and 10 (31%) HES patients presented with anemia and thrombocytopenia, respectively. A median peak of peripheral blood eosinophilia was 13.9×10^9/l (range, 2.5–87.4×10^9/l) whereas bone marrow was occupied by eosinophils (median, 40%; range, 7%–80%). Splenomegaly and pulmonary infiltrates were the most frequent organ involvement and were observed in 22 (68%) and 13 (41%) patients, respectively. The other eosinophilia-attributable organ manifestations involved the liver (n = 11; 34%), skin (n = 5; 16%), lymph nodes (n = 5; 16%), heart (n = 5; 16%), central nervous system (n = 4; 12%), gastrointestinal tract (n = 2; 6%) and joints (n = 1; 3%). Eleven patients were asymptomatic at diagnosis and blood eosinophilia was detected accidentally on routine blood examination. A total of 26 patients received IM at the starting dose of 100 mg/d, the remaining 6 individuals were treated with a daily dose of 400 mg. All patients achieved peripheral blood normalization of eosinophilia after median (range) of 20 (4–120) days of IM therapy. All symptomatic patients presented resolution of organ damage within the first 3 months of IM therapy. Complete molecular response was attained in all treated patients after median (range) of 9 (1–51) months. There was no difference in time to achieve CHR and CMR between patients receiving initial IM at 100 mg and 400 mg a day. The maintained IM dose varies from 400 mg daily to 100 mg weekly.

The updated information on long-term follow-up was reported for 22 patients. Median (range) time on IM was 11.9 (2.3–15.1) years. The median (range) duration of CHR and CMR was 11.5 (1.6–17.5) years and 9.8 (1–17) years, respectively. None of the patients exhibited IM resistance during treatment or had transformation into acute myeloid leukemia. No relevant side effects of IM were observed. Seven patients discontinued IM therapy after achieving long-term CHR and CMR, but disease relapse was demonstrated in 5 of them within 12 months after treatment cessation. In these patients, second CHR and CMR were obtained after IM reinitiation. Two patients have remained in remission for over 7 years after IM cessation. At the last follow-up visit, 21 out of 22 patients were alive, 1 patient died due to cardiac failure while being in CHR and CMR.

Discussion We present our data on IM treatment in patients with F/P-mutated HES. Our previous report on this topic was published several years ago,[6] and now the results have been updated after more than a decade of IM therapy. Our data confirm with high confidence that the effectiveness of IM treatment over time remains excellent. Moreover, in a small proportion of patients, the molecular response is durable despite IM discontinuation. The benefit of IM for F/P-mutated HES has been confirmed in numerous studies; however, both the initial and maintained IM doses differ between centers.[7-9] Based on our long-term experience as well as that of many other HES researchers,[7-11] we may conclude that IM at a starting dose of 100 mg daily is sufficient to induce hematological and molecular response. As a response maintenance, weekly doses of IM (100–200 mg) seem to be effective. Although in-depth molecular response occurs in the majority of F/P-mutated HES patients, IM discontinuation usually leads to disease recurrence. One can estimate that approximately 30% to 50% of patients can achieve durable effect after IM cessation; however, whether this strategy can be used in daily practice is still unknown and requires confirmation in further studies.[8,10] Interestingly, prompt IM reinitiation led to second remission in most cases. In our study cohort, 7 patients stopped IM after achieving CMR[11]; however, only 2 of them maintained the response at the last medical contact. These 2 patients have been now IM-free for more than 7 years and still remain in CMR. However, the factors predicting the maintenance of durable response after treatment discontinuation have not been defined so far.

It is worth noting that PubMed database search for the terms "imatinib", "*FIP1L1-PDGFRA*", and "hypereosinophilic syndrome" revealed no studies published in the past 3 years concerning IM use in HES, except for case reports.

The number of patients with HES treated with IM and treatment efficacy were both comparable with the results published elsewhere[7-10]; however, our follow-up period was significantly longer (TABLE 1). All study groups reported an excellent response to IM, nonetheless single cases of IM resistance or transformation into acute myeloid leukemia may occur.[8-10] Of note, treatment with a low IM dose remains extremely safe and cost-effective. The latter is especially true when generic IM is administered, which is now a common practice. However, the role of generic IM in therapy of F/P-mutated HES has not been evaluated so far. Our confidence in effectiveness of generic IM in HES is based on our own experience with a variety of generics as well as on results reported for patients with chronic myeloid leukemia.[12] Nevertheless, such analysis regarding the F/P-mutated HES population is needed.

In conclusion, our results have confirmed a very long-term efficacy and safety of both branded and generic IM in patients with F/P-associated HES. Discontinuation of IM is successful in about 30% of patients and can be attempted after careful assessment of risk-to-benefit ratio in experienced centers.

ARTICLE INFORMATION

NOTE Digital identifiers were assigned to GH (ORCID iD, https://orcid.org/0000-0003-3703-1268) and KL (ORCID iD, https://orcid.org/0000-0003-0992-2020).

CONFLICT OF INTEREST None declared.

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