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Exquisite response to imatinib mesylate in \textit{FIP1L1-PDGFRA}-mutated hypereosinophilic syndrome: a very long-term experience of 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 $\geq 1.5 \times 10^9/l$ 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 $FIP1L1/PDGFR\alpha$ (Fip1-like1/platelet-derived growth factor receptor alpha, F/P) rearrangement was detected in approximately 10%-20% of patients with HES [2]. The widespread recognition of the growing number of molecular abnormalities in eosinophilia-related disorders, resulted in creation of a new category within the 2008 World Health Organization (WHO) classification: myeloid and lymphoid neoplasms with eosinophilia and rearrangements of $PDGFR\alpha$ (mainly F/P), $PDGFR(\beta)B$ 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 (RT-PCR) or fluorescence in situ hybridization (FISH) 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 (TK) and shows an excellent sensitivity to TK inhibitor- imatinib mesylate (IM) [2].

For unknown reason, the vast 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%-50%, mainly due to the irreversible cardiac failure [5].

Herein, we update our very long-term 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.
Material and methods

We evaluated the demographics, clinical and laboratory data as well as long-term results of IM treatment in F/P-mutated HES patients from several polish institutions. The first patient was recruited in 2003 and the last initiated the treatment in 2017. IM starting and maintained doses were left to physician’s discretion and institution’s policy, however a weekly IM dose was recommended as an end-point. Patients in whom F/P-mutated HES was diagnosed before 2014 received branded IM (Glivec®, Novartis) and then were consequently switched to one of the generics available on the market. Those who were diagnosed after 2014, received generic IM as a frontline therapy. Discontinuation of IM was recommended for patients who achieved durable (at least 2 years duration) in-depth molecular remission. RT-PCR 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 3-6 months and then yearly. Complete hematological response (CHR) was defined as normalization (<0.7x10⁹/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 IM commencement. Undetectable F/P rearrangement on PCR 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

Thirty-two patients (30 male and 2 female) meeting the HES criteria [1] and harboring the FIP1L1/PDGFRA transcript were included in this analysis. The median age was 51 years (range 19-80). At diagnosis, 14 (44%) and 10 (31%) HES patients manifested with anemia and thrombocytopenia, respectively. A median peak of peripheral blood eosinophilia was 13.9x10⁹/l (range 2.5-87.4) whereas bone marrow was occupied by eosinophils in median of
40% (range 7-80). Splenomegaly and pulmonary infiltrates were the most frequent organ involvement and included 22 (68%) and 13 (41%) patients, respectively. The other eosinophilia-attributable organ manifestations involved 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. Twenty-six patients received IM at the starting dose of 100 mg a day, the remaining 6 individuals were treated with a daily dose of 400 mg. 100% of patients achieved peripheral blood normalization of eosinophilia after median of 20 days (range 4-120) of IM therapy. All symptomatic patients presented resolution of organ damage within the first 3 months of IM. CMR was attained in 100% of treated patients after median of 9 months (range 1-51). 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 400mg daily to 100mg weekly.

The updated information on long-term follow-up was reported for 22 patients. Median time on IM was 11.9 years (range 2.3-15.1). The median duration of CHR and CMR was 11.5 years (range 1.6-17.5) and 9.8 years (range 1.0-17.0), respectively. None of the patients exhibited IM resistance during the period of treatment or had transformation into acute myeloid leukemia (AML). No relevant sides 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 re-initiation. Two patients remain in remission for over 7 years after IM stoppage. At the last contact, 21 out of 22 patients are alive, one 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 decade of IM therapy. Our data strongly confirm that over time the effectiveness of IM treatment 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 long-term experience of ours and many other HES researchers, we may conclude that IM at starting dose of 100mg daily is sufficient to induce hematological and molecular response. As a response maintenance, weekly doses of IM (100-200mg) seems to be effective. Although, in-depth molecular response occurs in overwhelming of F/P-mutated HES patients, IM discontinuation usually leads to disease recurrence. One can estimate that approximately 30%-50% of patients can achieve durable effect after IM cessation, however whether this procedure can be used in daily practice is still unknown and requires confirmation in further studies [8, 10].

Interestingly, prompt IM re-initiation led to second remission in most cases. In our study cohort, seven patients stopped IM after achieving CMR [11], however only 2 of them maintains the response at the last contact. These 2 patients have been now more than 7 years IM-free 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 despite case reports, not a single study has been published in the past 3 years concerning IM use in the HES when searching PubMed database for term containing “imatinib; FIP1L1-PDGFRα; hypereosinophilic syndrome”.

The number of HES patients treated with IM and its efficacy were both comparable to the results published elsewhere [7-10], however our follow-up period was significantly longer (Table 1). All study groups have reported an excellent response to IM, nonetheless single cases of IM resistance or transformation into AML may occur [8-10]. Of note is that the
treatment with 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 on effectiveness of generic IM in HES is based on our own experience with variety of generics as well as on results reported for patients with chronic myeloid leukemia [12]. Nevertheless, such analysis regarding 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. IM discontinuation is successful in about 30% of patients and can be attempted after careful assessment of risk/benefit ratio in experienced centers.
References


Table 1. Large studies with imatinib mesylate for *FIP1L1-PDGFRα*-mutated hypereosinophilic syndrome

<table>
<thead>
<tr>
<th>Number of included patients</th>
<th>Complete hematological response rate (%)</th>
<th>Complete molecular response rate (%)</th>
<th>Median duration of follow-up (years)</th>
<th>References/year of publication</th>
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<td>16</td>
<td>95</td>
<td>87</td>
<td>1.8</td>
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<td>100</td>
<td>95</td>
<td>4.3</td>
<td>8/2013</td>
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<td>6.0</td>
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<td>33</td>
<td>94</td>
<td>97</td>
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<td>32</td>
<td>100</td>
<td>100</td>
<td>11.9 (22 patients)</td>
<td>This study</td>
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