

# The Spectrum of FIP1L1-PDGFR $\alpha$ -Associated Chronic Eosinophilic Leukemia

## New Insights Based on a Survey of 44 Cases

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**Abstract:** Imatinib is the treatment of choice for FIP1L1/PDGFR $\alpha$  (F/P)-associated chronic eosinophilic leukemia (F/P<sup>+</sup> CEL), but its optimal dosing, duration, and possibility of discontinuation are still a matter of debate. A retrospective multicenter study was conducted with 44 F/P<sup>+</sup> CEL patients identified in the French Eosinophil Network and treated with imatinib. The most frequently involved systems were skin (57%), spleen (52%), and lung (45%), and eosinophilic heart disease was observed in 15 patients (34%). Complete hematologic response (CHR) was obtained in all patients, and complete molecular response (CMR) in 95% of patients (average initial imatinib dose, 165 mg/d). For 29 patients the imatinib dose was tapered with a maintenance dose of 58 mg/d ( $\pm$ 34 mg/d), allowing sustained CHR and CMR. None of the patients developed resistance during a median follow-up of 52.3 months (range, 1.4–97.4 mo). Imatinib was stopped in 11 patients; 6 of the patients subsequently relapsed, but 5 remained in persistent CHR or CMR (range,

9–88 mo). These results confirm that an initial low-dose regimen of imatinib (100 mg/d) followed by a lower maintenance dose can be efficient for obtaining long-term CHR and CMR. Our data also suggest that imatinib can be stopped in some patients without molecular relapse.

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**Abbreviations:** ABL = Abelson, CEL = chronic eosinophilic leukemia, CHR = complete hematologic response, CML = chronic myelogenous leukemia, CMR = complete molecular response, CT = computed tomography, FIP1L1-PDGFR $\alpha$  = Fip1-like1-platelet-derived growth factor receptor alpha gene, FISH = fluorescence in situ hybridization, F/P<sup>+</sup> CEL = FIP1L1-PDGFR $\alpha$ -associated chronic eosinophilic leukemia, HES = hypereosinophilic syndrome, ID = initial dose, IgE = immunoglobulin E, I-HES = lymphocytic hypereosinophilic syndrome, MD = maintenance dose, MRI = magnetic resonance imaging, ROC = receiver operating characteristic, RQ-PCR = real-time quantitative reverse transcription polymerase chain reaction, RT-PCR = reverse transcription polymerase chain reaction, TCR = T-cell receptor, u-HES = undefined hypereosinophilic syndrome, WT1 = Wilms tumor gene.

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## INTRODUCTION

The fusion gene FIP1L1-PDGFR $\alpha$  (F/P) is the most frequent clonal event identified in hypereosinophilic syndrome (HES),<sup>5,27</sup> a rare hematologic disorder characterized by chronic, unexplained eosinophilia greater than 1500/mm<sup>3</sup>. According to the World Health Organization (WHO) classification of myeloproliferative neoplasms, this variant of HES is now considered a chronic eosinophilic leukemia (CEL)<sup>29</sup> in which eosinophil proliferation is directly related to enhanced kinase activity of PDGFR $\alpha$  induced by the fusion gene.

Although reliable epidemiologic studies are lacking, the incidence of F/P fusion in developed countries is approximately 10%–20% (range, 3%–56%) in patients with unexplained hypereosinophilia.<sup>8</sup> Only a few studies with a limited number of patients have reported a complete picture of this leukemia.<sup>14,28</sup> However, some features associated with F/P<sup>+</sup> CEL have already been described. Male predominance, cardiac involvement, and hepatosplenomegaly are common findings in F/P<sup>+</sup> CEL.<sup>14,20</sup> Vitamin B12 and tryptase are frequently elevated in this condition and may be useful diagnostic biomarkers.<sup>14</sup> The Wilms tumor gene (WT1) is over-expressed at various levels in different hematologic malignancies, including F/P<sup>+</sup> CEL. Cilloni et al<sup>3</sup>

reported that the amount of WT1 transcript allows discrimination between secondary and reactive eosinophilia from HES or CEL.

Originally developed for the treatment of chronic myelogenous leukemia (CML),<sup>6</sup> imatinib targets different tyrosine kinases, including FIP1L1-PDGFR $\alpha$ , whose constitutive kinase activity is 100-fold more sensitive as a target for imatinib than BCR-ABL.<sup>5</sup> Thus, imatinib has revolutionized the therapy F/P<sup>+</sup> CEL.<sup>1,13,20,22</sup> However, the imatinib regimen for F/P<sup>+</sup> CEL is still a matter of debate, concerning both the initial dose (100 mg/d vs. 400 mg/d) and the safety of maintenance using a reduced dose (100 mg/wk).<sup>11</sup> Imatinib is able to control F/P<sup>+</sup> CEL over the long-term. Nevertheless, based on a single study showing relapse for each of 5 patients after discontinuation of imatinib, it is recommended that patients continue imatinib to avoid loss of response or relapse.<sup>15</sup>

The significance of these observations is impaired by the small number of patients reported in previous studies, resulting in a truncated view of the pathology. In addition, to our knowledge no study has evaluated all of these clinical, laboratory, and therapeutic parameters in a single cohort of patients. To better define the spectrum of F/P<sup>+</sup> CEL and describe the main characteristics and outcomes of this rare condition, a survey was initiated in 2010 through the French Eosinophil Network. We report here data from 44 patients with F/P<sup>+</sup> CEL.

## METHODS

### Patients

This retrospective survey was initiated by the French Eosinophil Network, which comprises 27 university and general hospitals all over France. The study was approved by the Lille Hospital ethical committee and carried out in accordance with the Helsinki convention. All consecutive HES patients with a documented presence of the FIP1L1-PDGFR $\alpha$  fusion gene since 2003 were included in the study. Clinical and laboratory data were recorded by the practitioners in charge of the patients using a standardized form. Clinical involvement of the heart, lungs, gastrointestinal tract, liver, spleen, skin, peripheral or central nervous system, and thrombosis was highlighted. Hepatomegaly and splenomegaly were systematically considered clinically relevant regarding computed tomography (CT) and/or magnetic resonance imaging (MRI). Eosinophilic cardiopathy was assessed in all patients using electrocardiography and echocardiography.

Common laboratory parameters previously shown or suspected to be useful markers of F/P<sup>+</sup> CEL (for example, peak eosinophil count, serum total IgE, vitamin B12, and tryptase levels) were assessed locally. Peripheral T-cell analysis, including T-cell immunophenotype and analysis of T-cell receptor (TCR) gamma and delta chain rearrangements, was performed at University Hospital of Lille as described previously.<sup>26</sup>

### FIP1L1-PDGFR $\alpha$ Screening

Briefly, RNA was isolated from peripheral blood mononuclear cells according to the tri-phasic extraction method (Tri-reagent method). Reverse transcription (RT) was performed using the High Capacity cDNA Archive Kit (Applied Biosystems, Foster City, CA). ABL1 was used as a control gene. F/P fusion transcript was screened in 2 French laboratories (University Hospital of Lille and University Hospital of Saint-Louis) by nested RT-polymerase chain reaction (RT-PCR) using the previously reported primers<sup>5</sup> and with 35 cycles for both PCR rounds. In patients in whom imatinib was stopped and complete hematologic response (CHR) maintained, real-time quantitative RT-PCR (RQ-PCR) (see **Figure S1, Supplemental Digital Content**,

<http://links.lww.com/MD/A22>) was performed in the laboratory of the University Hospital of Necker-Enfants Malades to determine that the fusion transcript remained undetectable.

### Analysis of WT1 Transcript Levels

To evaluate the potential usefulness of WT1 expression in F/P<sup>+</sup> CEL, WT1 transcript levels were assessed by RQ-PCR at the time of diagnosis in different groups of patients with eosinophilia: F/P<sup>+</sup> CEL, lymphocytic-HES (l-HES), undefined-HES (u-HES) (according to recent classification<sup>27</sup>), secondary eosinophilia, and hypereosinophilia with myeloid neoplasms (see **Table S1, Supplemental Digital Content**, <http://links.lww.com/MD/A19>). RQ-PCR assays were performed in the Lille laboratory on an ABI PRISM 7900 with Sequence Detection System (PE Applied Biosystems, Foster City, CA) according to the recommendations of the European LeukemiaNet.<sup>4</sup> WT1 transcript levels were normalized with respect to the number of ABL1 transcripts and expressed as the WT1 copy number for every 100 copies of ABL1 (%). WT1 was considered to be over-expressed at values higher than 0.5% in peripheral blood.

### Response to Treatment

The imatinib regimen was defined as follows: the first dose of imatinib received by the patient until the first change in dosage was recorded as the initial dose (ID). All doses after the ID were recorded as maintenance doses (MDs). To assess treatment efficacy, the following criteria were used: CHR was defined as a decrease in the absolute eosinophil count below the normal range (<500/mm<sup>3</sup>). CMR was defined as a negative RT-PCR and/or RQ-PCR assay for the F/P rearrangement. Hematologic relapse was defined as absolute eosinophil count beyond the upper normal range without another explanation.

### Statistical Analysis

The Mann-Whitney test was used to compare WT1 expression levels in 3 groups of patients: patients with HES, secondary eosinophilia, and eosinophilia associated with a myeloid neoplasm.  $P < 0.05$  was considered significant. Statistical analyses were performed using MedCalc software. Time to relapse was measured from the date of imatinib discontinuation to the date of relapse (hematologic and/or molecular) or the date of the last molecular examination for patients who did not relapse. We estimated relapse-free survival using the Kaplan-Meier method.

## RESULTS

### Patient Characteristics

We collected clinical and laboratory data from 44 patients with F/P<sup>+</sup> CEL diagnosed between 2003 and September 2011 (Table 1; see **Table S1, Supplemental Digital Content**, <http://links.lww.com/MD/A19>). The F/P fusion was demonstrated by RT-PCR in all cases but 1. Ten cases, including the patient with a negative RT-PCR, were confirmed by fluorescence in situ hybridization (FISH). Pretreatment bone marrow standard karyotypes were performed in 22 of 44 patients and did not reveal any additional cytogenetic abnormality in any of the patients studied. Median age at diagnosis was 41 years (range, 6–67 yr). With the exception of a 6-year-old girl, F/P was detected only in adult male patients. The median delay between the first finding of eosinophilia and therapeutic care was 17.6 months (range, 6–31 mo). Eosinophilia discovery was fortuitous for 4 asymptomatic patients, whereas most patients (40/44) presented with signs of end-organ involvement (Figure 1). Clinical characteristics are provided in Table 2 and Figure 2.

Anemia and/or thrombocytopenia was observed in 52% of cases. Vitamin B12 and tryptase levels were elevated in

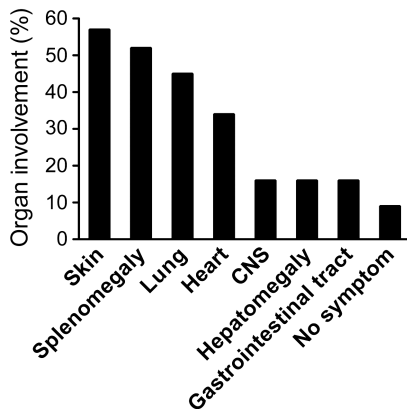
**TABLE 1.** Demographic, Laboratory, and Therapeutic Characteristics of F/P+ CEL Patients (n=44)

Characteristic	No. of Patients (%)
Age at eosinophilia onset, yr	
Median	41
Range	6–67
Sex ratio (M/F)	43/1
Duration of follow-up, mo	
Median	57.8
Range	6.6–318
Laboratory findings	
Anemia	16 (37)
Thrombocytopenia	16 (37)
$\gamma\delta$ TCR clonality (n=35)	8 (23)
T-cell abnormal phenotype	2 (5)
Increased Vitamin B12 (n=34)	28 (82)
Increased tryptase (n= 27)	21 (78)
Increased IgE <sub>Total</sub> (n=32)	5 (16)
Eosinophilia <sub>max</sub> (/mm <sup>3</sup> )	
Median	10,100
Range	1910–36,920
Therapeutic	
Corticosteroid use	14 (32)
CHR on corticosteroid	0 (0)
Other treatment	11 (25)
Imatinib	
Monotherapy when introduced	35 (80)
1st-line of treatment	26 (59)
2nd-line of treatment	10 (23)
3rd-line of treatment	7 (16)
5th-line of treatment	1 (2)
Imatinib follow-up, mo	
Median	52.4
Range	1.4–97.4

**TABLE 2.** Clinical Characteristics of F/P+ CEL Patients (n=44)

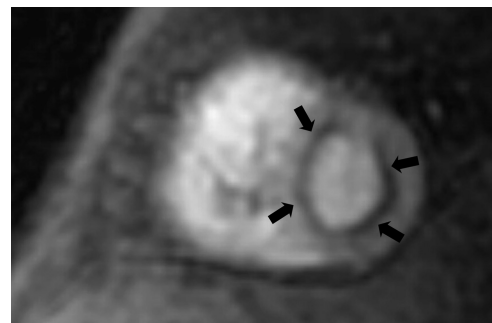
Characteristic	No. of Patients (%)
General symptoms	
Fatigue	16 (36)
Weight loss	12 (27)
Myalgia and/or arthralgia	5 (11)
Fever	1 (2)
Cardiac involvement	15 (34)
Valvular regurgitation	5 (11)
Myocarditis	3 (7)
Endomyocardial fibrosis	7 (16)
Left intraventricular thrombosis	3 (7)
Other	2 (5)
Cutaneous manifestations	25 (57)
Nodules	9 (20)
Pruritus	7 (16)
Dermographism	5 (11)
Mouth ulcers	3 (7)
Purpura	2 (5)
Splinter nails hemorrhage	2 (5)
Folliculitis	1 (2)
Erythema	1 (2)
Pulmonary symptoms	20 (46)
Chronic cough	18 (41)
Interstitial pneumonia	3 (7)
Gastrointestinal tract	7 (16)
Abdominal pain	3 (7)
Diarrhea	6 (14)
Central nervous system	7 (16)
With cardiac involvement	5 (11)
Without cardiac involvement	2 (5)
Peripheral nervous system	0
Hepatomegaly	7 (16)
Splenomegaly	23 (52)

82% and 78% of patients, respectively (see Table 1). Total IgE levels were normal in 27 of 32 patients. T-cell abnormalities were observed in 8 of 35 (23%) examined cases, but were limited to a clonal rearrangement of the TCR $\gamma$  gene in 6 patients. Two

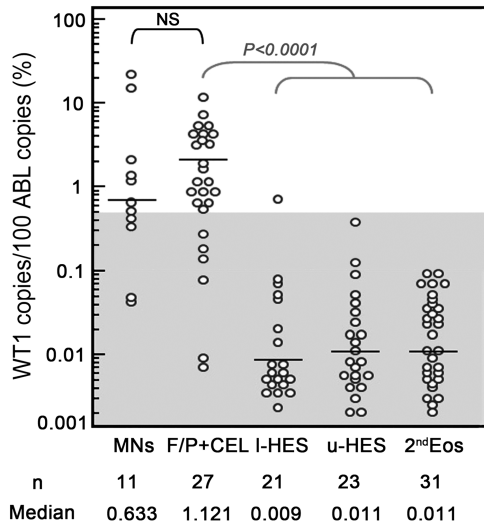


**FIGURE 1.** Pattern of organ involvement in F/P+ CEL. The frequency of clinical symptoms is expressed as a percentage of the entire cohort (n = 44). Abbreviation: CNS = central nervous system.

patients had abnormal peripheral T-cell populations with a clonal TCR rearrangement: 1 with a CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup>CD7<sup>-</sup> (33% of total lymphocytes) population with V $\gamma$ IJ1J2, V $\gamma$ 9J1J2, and V $\gamma$ 10J1J2 rearrangements, and the other with a CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup>CD7<sup>+</sup> (14%) population associated with V $\gamma$ IJ2J2 and V $\gamma$ 9J1J2 clonal rearrangements (see **Figure S2, Supplemental Digital Content**, <http://links.lww.com/MD/A23>; and **Table S2, Supplemental Digital Content**, <http://links.lww.com/MD/A20>).



**FIGURE 2.** Cardiac MRI of eosinophilic endomyocardial fibrosis: first-pass perfusion imaging shows an inner rim of nonenhancing of the left ventricle (black arrow) corresponding to endomyocardial fibrosis.



**FIGURE 3.** Peripheral blood WT1 transcript levels in various hypereosinophilic conditions. Blood expression of WT1 evaluated at diagnosis is shown for each patient (o), and the bars indicate the means. The grey zone represents the normal expression level of WT1 in healthy subjects. Population characteristics are summarized in **Table S1, Supplemental Digital Content**, <http://links.lww.com/MD/A19>. Abbreviations: 2nd Eos = secondary eosinophilia, ABL = Abelson, F/P<sup>+</sup> CEL = FIP1L1-PDGFRA chronic eosinophilic leukemia, I-HES = lymphocytic hypereosinophilic syndrome, MNs = myeloid neoplasms, u-HES = undefined hypereosinophilic syndrome, WT1 = Wilms tumor gene.

Fourteen patients received corticosteroids as first-line therapy prior to imatinib, but none of them achieved CHR. Corticosteroids have always been given as a monotherapy. Eight patients received imatinib as second-line treatment. For the other 6 patients, treatment included hydroxyurea (n = 3), cyclophosphamide (n = 2), or etoposide (n = 1). Eleven patients received other therapies, 5 of whom never received corticosteroids (Table 2; see **Table S3, Supplemental Digital Content**, <http://links.lww.com/MD/A21>). Notably, only 1 patient (Patient 17) died suddenly of an undetermined cause, but without any suspected cardiac involvement, 1 month after starting imatinib (200 mg/d).

**Evaluation of WT1 Expression**

WT1 expression was evaluated in 27 patients with F/P<sup>+</sup> CEL, 21 patients with I-HES, 23 patients with u-HES, 31 patients with secondary eosinophilia, and 11 patients with myeloid neoplasms with or without eosinophilia (Figure 3; see **Table S1, Supplemental Digital Content**, <http://links.lww.com/MD/A19>). WT1 transcript levels measured by RQ-PCR were significantly higher in F/P<sup>+</sup> CEL (median, 1.121%) compared to I-HES (0.009%), u-HES (0.011%), and reactive HE (0.011%, p < 0.0001). We found that 21 F/P<sup>+</sup> CEL patients (78%) over-expressed WT1 compared to 1 of the 49 (2%) I-HES and u-HES patients. However, no significant difference was observed between F/P<sup>+</sup> CEL patients and those with other myeloid neoplasms (median, 0.633%; p = 0.67). No correlation was observed between WT1 transcript levels and the percentage of cells harboring the 4q12 deletion in FISH analysis, absolute eosinophil count, total IgE, and serum tryptase (data not shown). We also evaluated the diagnostic value of over-expression of WT1 in F/P<sup>+</sup> HES and F/P<sup>-</sup> HES (I-HES and u-HES), and we compared this value to other laboratory markers classically used for HES diagnosis (that is, vitamin B12, tryptase, total IgE, and absolute eosinophil count). Receiver operating characteristic (ROC) curves showed good diagnostic values for all of the studied parameters, with AUC > 0.85 and sensitivity and specificity both >84%, with threshold values calculated close to routinely used values, except for the absolute eosinophil count (threshold 5000/mm<sup>3</sup>) (see **Figure S3, Supplemental Digital Content**, <http://links.lww.com/MD/A24>). Nevertheless, the statistic comparison of ROC curves did not reveal a significant difference between the studied markers. WT1 expression was finally evaluated before and after imatinib intake in 3 F/P<sup>+</sup> CEL patients. In all 3 patients, WT1 expression normalized concomitantly with the achievement of CHR and CMR (data not shown).

**Initial Imatinib Dose**

Imatinib was the first-line therapy in 26 patients and was given as monotherapy, with the exception of 2 patients who required corticosteroids for acute myocarditis before imatinib. The median follow-up of imatinib therapy was 52.4 months (range, 1.4–97.4 mo), with the first patients treated in 2003.

Response rates were evaluated in 43 patients, excluding the patient who died (Table 3). The ID of imatinib ranged from

**TABLE 3.** Dose and Response to Imatinib Treatment

Dosage of Imatinib	n	Mean Dose	CHR	CMR
<b>Initial dose</b>				
400 mg/d	8	165 mg/d (n=44)	98% (42/43)	95% (18/19)
300 mg/d	1			
200 mg/d	2			
150 mg/d	1			
100 mg/d	32			
<b>Maintenance dose</b>				
200 mg/d	1	58 mg/d (n=29)	100% (29/29)	100% (14/14)
100 mg/d	4			
50 mg/d*	18			
<50 mg/d†	6			

CHR and CMR are expressed as percentages of evaluable patients.

\*50 mg daily or 100 mg/2 d.

†Imatinib doses <50 mg daily corresponding to 100 mg once a week (14.3 mg/d), 100 mg every 5 days (20 mg/d), 150 mg per week (21.4 mg/d), or 100 mg every 3 days (33.3 mg/d).

100 to 400 mg/d (mean, 165 ± 117 mg/d). An ID of 100 mg/d was given to the majority of patients (32/44). During the initial phase, CHR was observed in all cases but 1 (42/43, 97.7%). CHR was not achieved in 1 patient (Patient 15) with an ID of 100 mg/d after 1 month, but an increased dosage up to 200 mg/d induced CHR. Despite variable times for hematologic testing, CHR was achieved rapidly (<15 d in 22 patients) (see **Table S2, Supplemental Digital Content**, <http://links.lww.com/MD/A20>). CMR was achieved in 18 of the 19 patients tested during the ID phase. As for CHR, and due to the retrospective nature of this study, CMR was evaluated at various times during the ID phase. Nevertheless, we observed that CMR was achieved rapidly in 2 patients (20 and 14 d after the beginning of imatinib treatment in Patients 10 and 39, respectively). In some cases, CMR was obtained after a longer period of therapy, up to 4 months in Patient 13. Only 1 patient in our cohort, a 6-year-old girl (Patient 14), did not achieve CMR after 4 months of imatinib therapy, despite achieving CHR.

Although transient myocarditis has been described after the initiation of imatinib, we did not observe such an adverse event in the 15 patients with cardiac involvement identified prior to imatinib therapy, whereas only 2 were concomitantly treated with corticosteroids.

### Reduction of Imatinib Dose

The imatinib dose was reduced in 29 patients of the cohort after a median ID duration of 6.2 months (range, 0.1–64.1 mo) (see Table 3 and Figure 4). Several regimen schedules were used and the MD expressed as the equivalent daily dose. The MD ranged from 14.3 mg (100 mg/wk) to 200 mg/d, and for most patients (18/29) consisted of 50 mg/d (100 mg every 2 d). The mean daily dose from ID to MD decreased from 165 mg/d (±117 mg/d) to 58 mg/d (±34 mg/d). Regardless of the MD, it allowed the maintenance of CHR (100%, 29/29 patients) and CMR (100%, 14/14 patients; see Table 3). None of the 29 patients developed resistance to imatinib with a median follow-up (ID + MD) of 52.4 months (range, 1.4–97.4 mo).

The individual imatinib scheduling and molecular testing during imatinib therapy in the 44 patients are provided in Figure 5. The time needed to achieve CMR was longer than the time needed to achieve CHR. Among the 35 different patients tested

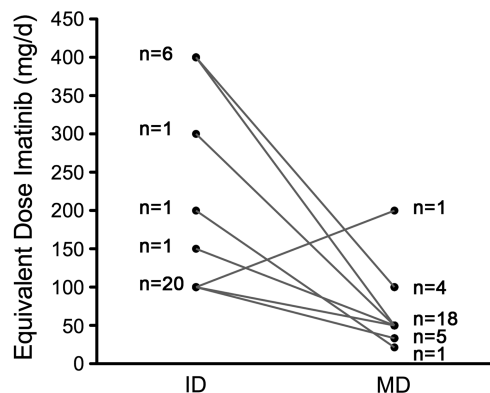
for the F/P transcript during ID or MD, only 2 patients achieved CMR at their first molecular testing. For Patient 13, the nested PCR for F/P remained positive after 4 months of imatinib (400 mg/d) treatment and then became undetectable after 9 months of the same regimen. Further dose de-escalation to 100 mg/d allowed the maintenance of molecular remission. For Patient 14, RQ-PCR was positive twice (at 3 and 4 mo of imatinib therapy), and she was further treated by allogeneic bone marrow transplantation, allowing persistent CHR and CMR with a follow-up of 60 months.

### Discontinuation of Imatinib

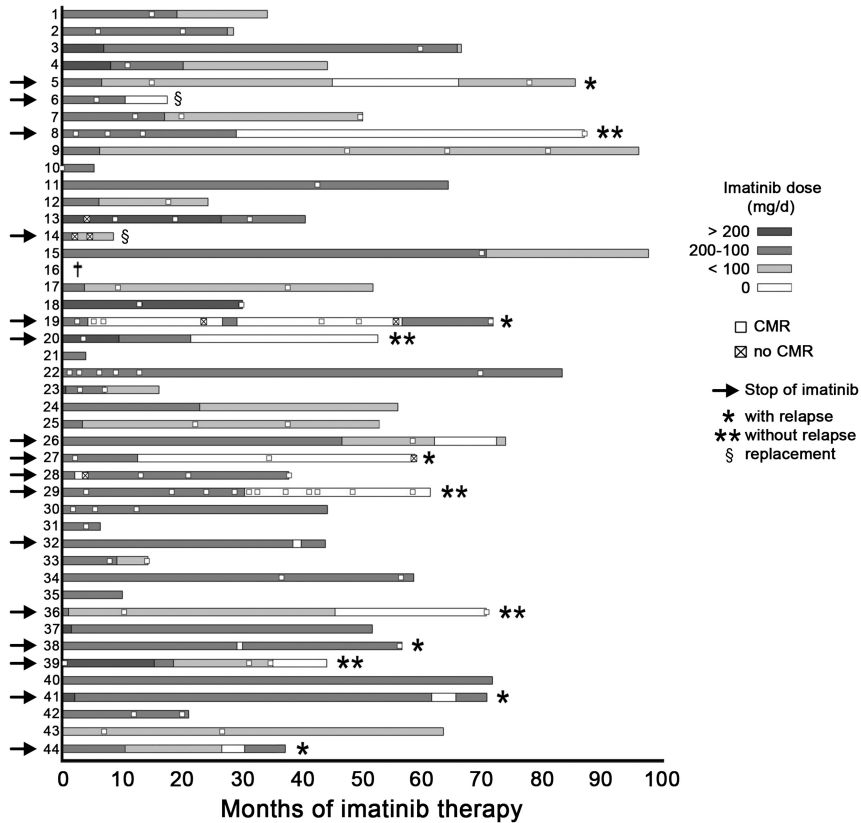
Transient or long-term discontinuation of imatinib was noted in 16 patients (see Figure 5). Imatinib treatment was ceased in 4 patients due to adverse events. Two patients (Patients 6, 27) experienced imatinib-induced hepatitis, which resolved after permanent discontinuation of imatinib. In a third patient (Patient 32), imatinib was temporarily stopped (6 wk) due to abnormal liver enzyme levels that returned to normal despite the reintroduction of imatinib. An unexplained papillary edema was the last adverse event leading to definitive discontinuation of imatinib (Patient 39). Other reasons for discontinuation were a lack of compliance (n = 3), medical decisions (n = 7), desire for fatherhood (n = 1), and possible failure of imatinib therapy (Patient 14).

In 2 cases imatinib was successfully replaced by nilotinib (Patient 6) or bone marrow transplantation (Patient 14). Three patients had only a transient cessation of imatinib therapy without hematologic relapse. All 11 of the remaining patients with prolonged discontinuation of imatinib were in CHR when imatinib was stopped, and in CMR for all of the 8 tested patients. Six patients (55%) experienced hematologic and/or molecular relapses (Patients 5, 19, 27, 38, 41, 44). The median dose of imatinib before discontinuation was 100 mg/d (range, 14.3–100.0 mg/d). The hematologic relapses (confirmed or not by molecular analysis) occurred after various time intervals, ranging from 1 (Patient 38) to more than 27 months (Patient 19). One patient experienced 2 stops in imatinib therapy after sustained hematologic and molecular periods of remission of more than 2 years, but molecular relapses occurred each time (Patient 19). It is noteworthy that the second molecular relapse (without hematologic relapse) was identified 27 months after discontinuation of imatinib, whereas 2 previous molecular tests after 14 and 21 months of imatinib therapy were negative (see Figure 5). In 5 cases, reinitiation of imatinib induced CHR and/or CMR, with the same dose as before discontinuation in 3 of 5 patients. One patient with imatinib-induced hepatitis refused to switch to another tyrosine kinase inhibitor and remained in hematologic and molecular relapse, without end-organ involvement (Patient 27).

More importantly, 5 patients (Patients 8, 20, 29, 36, 39) discontinued imatinib without hematologic relapse after a median follow-up of 31 months (range, 9–88 mo). With the exception of 1 patient who could not be tested (Patient 20), remission was confirmed at the molecular level by negative RT-PCR in the 4 remaining patients (see Figure 5). Consistent with the results of nested RT-PCR, the fusion transcript F/P became undetectable by RQ-PCR in 3 patients, and remained detectable at very low levels in only 1 patient (Patient 8). Two of the patients received an ID of 100 mg/d imatinib, 1 received 200 mg/d, and 2 others 400 mg/d. The median duration of treatment before discontinuation of imatinib was 30.2 months (range, 21.3–45.5 mo), which was not significantly different than that observed in relapsing patients (median, 38.3 mo; range, 4.2–61.9 mo). Thus, relapse-free survival in the 11 patients who



**FIGURE 4.** Simplified pattern of imatinib dose de-escalation in F/P<sup>+</sup> CEL patients. The shift from the initial dose (ID) to a maintenance dose (MD) is represented for all patients who underwent de-escalation of the supporting dose (n = 29). The values given for each dose indicate the numbers of patients involved. The maintenance dose was the last identified, and doses were figured as a daily equivalent dose of imatinib.



**FIGURE 5.** Individual imatinib scheduling, follow-up, and molecular response during imatinib therapy. Imatinib doses are represented for individual patients by shaded bars (white indicates imatinib arrest). Complete molecular remission evaluated by nested RT-PCR is shown by white squares, and molecular relapse by black squares. \*Definitive arrest of imatinib without relapse; \*\*complete arrest of imatinib with hematologic and/or molecular relapse; §imatinib replaced by nilotinib (Patient 6) or bone marrow transplantation (Patient 14); †death.

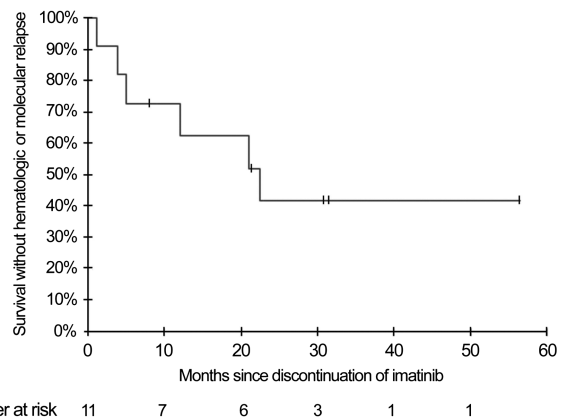
discontinued imatinib after achieving CHR was 61% at 1 year and 42% at 2 years (Figure 6).

**DISCUSSION**

HES encompasses a heterogeneous group of diseases characterized by chronic and unexplained eosinophilia with tissue damage. F/P+ CEL represents the myeloproliferative variant of HES. The current retrospective multicenter study, which included all consecutive patients with a documented presence of the F/P fusion gene since 2003, was coordinated by the French Eosinophil Network and represents the largest cohort of F/P+ CEL published to date, to our knowledge. This work provides a complete overview of the clinical and laboratory aspects of this disease, as well as the response to treatment.

Cardiac involvement, particularly endomyocardial fibrosis, is known to be a major prognostic factor in HES,<sup>16</sup> and its occurrence during HES has been revised downward with recent data suggesting a prevalence of 22% in F/P+ CEL and 19% in F/P<sup>-</sup> HES.<sup>20</sup> Previous studies reported a prevalence of approximately 50% in nonselected HES.<sup>30</sup> In 7 other retrospective series representing a total of 121 patients with F/P+ CEL, cardiac involvement was reported in only 26 patients (21%).<sup>1,3,5,9,18,21,28</sup> In the present study, heart involvement was systematically screened, identifying 15 patients (34%) with a specific eosinophilic cardiac disease. None of the patients died from cardiac failure, but 1 patient required heart transplantation and was still alive 22 months later with CHR and CMR of F/P+ CEL.

Therefore, we confirmed that eosinophilic cardiopathy is a frequent complication of F/P+ CEL that may have been underestimated in recent studies (with the exception of the National Institutes of Health [NIH] cohort in which 41% of 17 F/P+ CEL patients had cardiac injury), strongly suggesting a need for systematic screening, even in asymptomatic patients. The occurrence



**FIGURE 6.** Kaplan-Meier estimates of complete hematologic remission after the discontinuation of imatinib in 11 patients with FIP1L1-PDGFR<sup>a</sup> chronic eosinophilic leukemia.

of acute myocarditis after the initiation of imatinib therapy has been reported in F/P<sup>+</sup> CEL patients with cardiac involvement at diagnosis,<sup>23</sup> leading to the recommendation of systematic corticosteroid therapy in association with imatinib in untreated patients. However, the frequency of this complication seems low, as none of our 13 patients with eosinophilic cardiomyopathy who were treated with imatinib without corticosteroids developed such myocarditis.

The other most common manifestations were cutaneous (57%) and splenomegaly (52%), which is a common finding in myeloproliferative neoplasms. In contrast to the cutaneous involvement observed in lymphocytic- or undefined-HES, none of the F/P<sup>+</sup> patients had angioedema. The laboratory data are consistent with previous reports; 43/45 patients had elevated B12 and/or tryptase levels and/or normal total IgE levels. We confirmed the male predominance of F/P<sup>+</sup> CEL, with only 1 6-year-old girl affected. Though uncommon, such pediatric cases have been reported previously, emphasizing the need for F/P screening when confronted by unexplained eosinophilia in children.<sup>24,25</sup> To the best of our knowledge, fewer than 10 women harboring the F/P fusion have been described. This 1-sided sex ratio previously described in smaller series<sup>1,9,20,28</sup> is reminiscent of the male sex ratio observed in other myeloproliferative neoplasms and remains unexplained. However, 1 important consequence may be to primarily reserve F/P screening (by RT-PCR and/or FISH) to unexplained eosinophilia in men, particularly in the setting of high B12 and/or tryptase levels. The diagnosis of F/P<sup>+</sup> CEL remains unlikely in women with increased levels of total IgE. One other suggestive finding in F/P<sup>+</sup> CEL compared to other variants of HES is the absence of a hematologic response under corticosteroid therapy. Among the 13 patients treated with corticosteroids as first-line therapy, none had a complete or partial hematologic response (decreased absolute eosinophil count of more than 50%). Such resistance to steroids may justify imatinib therapy in men affected by a life-threatening and unexplained eosinophilia before getting the results of F/P screening.

$\gamma$ TCR gene rearrangements were detected in 8 of the 35 tested patients (23%). The significance of such clonal T cells without abnormal phenotypes remains uncertain and may correspond to clonal T cells harboring the F/P fusion, clonal antitumoral T cells, or false-positive results. This high frequency of clonal T cells in F/P<sup>+</sup> CEL that has already been reported<sup>7,9</sup> may raise doubts about the ability of TCR gene rearrangement screening to discriminate myeloproliferative and lymphocytic variants of HES.

More importantly, we describe here for the first time the presence of abnormal CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup> T cells in 2 patients (Patients 27, 43), comprising 33% and 14% of T cells, respectively, both with clonal rearrangements of the V $\gamma$ I and V $\gamma$ 9 chains (see **Figure S2, Supplemental Digital Content**, <http://links.lww.com/MD/A23>). Despite CHR and CMR with imatinib, these CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup> T cells persisted for more than 3 years in both patients. However, the properties of these T cells remain unknown; in particular, their ability to release interleukin-5 was not evaluated in the current study. These cases support the idea that the association of clonal TCR rearrangements with an abnormal phenotype is not sufficient to diagnose l-HES, and that an abnormal percentage of double-positive T cells may suggest the presence of F/P<sup>+</sup> CEL, whereas other abnormal phenotypes (for example, CD3<sup>+</sup>CD4<sup>+</sup>, CD3<sup>+</sup>CD4<sup>+</sup>CD7<sup>-</sup>, or CD3<sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup>) suggest l-HES.

WT1 over-expression is a useful marker for minimal residual disease monitoring in acute leukemia, especially in acute myeloid leukemia.<sup>12</sup> Conflicting data have been reported regarding the usefulness of WT1 as a diagnostic biomarker in HES.

Before the discovery of the F/P fusion gene, a study based on a small number of patients reported that the WT1 transcript level is high in eosinophilic leukemia and normal in HES.<sup>19</sup> A more recent study suggested that the WT1 transcript level is equally elevated in HES and F/P<sup>+</sup> CEL patients (peripheral blood or bone marrow), but it is normal in patients with reactive eosinophilia.<sup>3</sup> Our data strongly suggest that, in the context of eosinophilia, high WT1 expression in the peripheral blood is restricted to F/P<sup>+</sup> CEL. Therefore, a quantitative assessment of WT1 does not provide any additional information to discriminate between different variants of HES, and F/P testing alone may be sufficient to diagnose and follow-up F/P<sup>+</sup> CEL.

Due to its remarkable efficacy in the first uncontrolled studies,<sup>5</sup> the United States Food and Drug Administration and The European Medicines Agency approved imatinib for the treatment of F/P<sup>+</sup> CEL in the absence of a phase II study and randomized trial. Therefore, various dosages have been proposed in the literature, from 100 mg/d<sup>10,13,21</sup> to 400 mg/d.<sup>1,15</sup> Not surprisingly, imatinib displayed great efficiency in our study group. We confirmed that CHR and CMR occur regardless of the ID, especially that a low dose of 100 mg/d (given in 32 patients) is sufficient. An increase from 100 to 200 mg/d was required in only 1 patient after 1 month because of persistent eosinophilia. The only patient who did not achieve CMR was probably considered too early as a failure of imatinib (4 mo) and referred for bone marrow transplantation. This low ID offers the benefit of a well-tolerated treatment with no adverse event leading to discontinuation. As previously shown by Helbig et al<sup>11</sup> with a weekly dose of 100 to 200 mg, our results confirmed that a lower MD compared to the ID (mean, 58 mg/d vs. 165 mg/d) can sustain CHR and CMR. Finally, the ID and MD of imatinib led to CHR in 100% (43/43) of patients and CMR in 97% (33/34) of patients we evaluated, with a median follow-up of 52.4 months on therapy. We did not observe any case of primary or secondary resistance to imatinib, suggesting that additional F/P mutations, such as T674I or D842V, are a very rare complication, even in patients treated with low doses. Numerous biases related to the retrospective nature of the study do not allow us to propose a definitive therapeutic schedule for imatinib in F/P<sup>+</sup> CEL patients. However, we demonstrated that the most frequently used regimen in our cohort, an ID of 100 mg/d and MD of 50 mg/d is an efficient, safe, and cost-effective option.

To the best of our knowledge, this is the first report suggesting that discontinuation of imatinib may allow long-term imatinib-free CHR and CMR in F/P<sup>+</sup> CEL. In 2010, Mahon et al<sup>17</sup> demonstrated the feasibility of imatinib discontinuation in the chronic phase of CML in a prospective study, with 41% of the patients in persistent CMR at 12 months, which is in the same range as observations in the present study (45%). As observed in CML patients, the 6 F/P<sup>+</sup> CEL patients who experienced a molecular or hematologic relapse after discontinuation retained sensitivity to imatinib, suggesting that discontinuation does not lead to acquired resistance to imatinib or create a safety issue. A previous prospective study reported molecular relapse in 5 F/P<sup>+</sup> CEL patients who stopped imatinib after long-term CMR after 19–29 months of treatment.<sup>15</sup> As in CML,<sup>17</sup> relapse was defined by a semiquantitative RT-PCR assay soon (<5 mo) after imatinib discontinuation. The discrepancies between that study, in which all patients relapsed, and our findings remain unexplained and suggest that predictive factors associated with CMR need to be identified. The main concern about these results is the lack of validated criteria to define a CMR in F/P<sup>+</sup> CEL, and that we did not evaluate the possible persistence of bone marrow F/P<sup>+</sup> leukemic stem cells, as described

in CML despite CMR.<sup>2</sup> Until now, imatinib discontinuation was only to be considered within a clinical trial with strict molecular monitoring.

Overall, our findings confirm the high frequency of eosinophilic cardiopathy in F/P<sup>+</sup> CEL, which remains almost exclusively a male disorder. Low-dose imatinib in initiation (100 mg/d) and maintenance phases (100 mg every other d) is efficient and safe. Finally, our preliminary reports of maintained CMR after imatinib discontinuation may stimulate prospective trials to optimize the treatment of F/P<sup>+</sup> CEL.

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