RESEARCH LETTER

Cardiovascular dysfunction as a common cause of mortality in hypereosinophilic syndromes

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Introduction In 2008, a new classification of eosinophilic disorders has been proposed by the World Health Organization. A molecularly-defined category includes myeloid and lymphoid neoplasms with eosinophilia and genetic abnormalities within the platelet-derived growth factor receptor α (PDGFRA), platelet-derived growth factor receptor β, and fibroblast growth factor receptor 1.[1] The definition of idiopathic hypereosinophilic syndrome (HES) requires the exclusion of all primary and secondary causes of hypereosinophilia (HE). The diagnosis of idiopathic HES should be made when no underlying cause of HE is recognized and organ dysfunction is documented to be eosinophilia-related. A provisional term of HE of undetermined significance was proposed for patients with persistent idiopathic HE without organ damage.[2]

Survival rates for patients with HES have changed over the years. The introduction of tyrosine kinase inhibitor, imatinib, for the therapy of HES with detectable PDGFRA rearrangements has dramatically improved the long-term prognosis.[3] However, such a tremendous progress has not been demonstrated for patients with idiopathic HES (IHES). Only one large study presenting data on mortality in HES has been published in the past 25 years.[4]

Patients and methods We retrospectively evaluated demographic characteristics, clinical history, and treatment outcome of all patients receiving a diagnosis of HES in several hematologic institutions in Poland. The aim of the study was to report on the causes of death among patients with HES as well as to try to define the risk factors for overall survival. Our database of eosinophilic disorders is being completed on a regular basis and systematically verified. The following types of HES were included in our system: IHES, HES with *FIP1L1-PDGFRA* rearrangement (HES F/P+), and HE of undetermined significance. Before a patient entered the study, all medical records were verified again by a physician with expertise in the evaluation of HES (GH). In total, we identified 117 patients with different variants of HES: IHES (n = 48), HES F/P+ (n = 29), and HE of undetermined significance (n = 40). The maximum follow-up for the entire cohort was almost 30 years.

Statistical analysis Nonparametric comparisons of group means were performed using the Mann–Whitney test. Proportions were compared using the Fisher exact test. The distribution for overall survival was estimated using the Kaplan–Meier method and compared using the log-rank test. All variables with a *P* value of less than 0.1 in a univariate analysis were considered to be candidates for the stepwise Cox regression model. A *P* value of less than 0.05 was considered significant in a multivariate model. The Spearman rank correlation was used to identify associations between variables. All computations were performed using the StatSoft Poland analysis software (version 10.0).

Results Overall, 9 deaths were reported in 117 patients with HES (8%). No deaths were reported for patients with HES F/P+ and HE of undetermined significance after median follow-up periods of 8 and 5 years, respectively.

A median follow-up for the IHES population was 6.7 years (range, 0.01–29.1 years); median survival was not reached. The estimated overall survival was 80% at 10 years and 72% at 20 years (Supplementary material online, *Figure S1*).

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TABLE 1 Basic characteristics of alive and deceased patients with idiopathic hypereosinophilic syndromes

Parameter	HES-A (n = 39)	HES-D (n = 9)	*P* value
sex, male/female	22/17	7/2	NS
age at diagnosis, y	52 (19–83)	65 (43–73)	0.02
white blood cell count, 10^9/l	15.4 (5.5–120.0)	28.3 (3.9–32.4)	0.005
absolute eosinophil count, 10^9/l	7.2 (1.5–88.8)	13.8 (3.9–32.4)	0.04
hemoglobin, g/dl	12.8 (8.6–17.7)	12.6 (8.1–14.4)	NS
platelet count, 10^9/l	248 (47–833)	380 (31–1320)	NS
eosinophilia in the bone marrow, %	31 (14–80)	52 (40–65)	0.005
serum IgE, IU/ml	77 (2.7–24134)	151 (0.1–2087)	NS
serum vitamin B_{12}, pg/ml	438 (123–3115)	494 (250–2000)	NS

Data are presented as number or as median (interquartile range).

Abbreviations: HES-A, alive patients with idiopathic hypereosinophilic syndromes; HES-D, deceased patients with idiopathic hypereosinophilic syndromes; IgE, immunoglobulin E; NS, nonsignificant

Nine deaths were reported in patients with IHES (19%; 7 men, 2 women). A median age at diagnosis was 65 years. A median time from diagnosis to death in this patient cohort was 3 months (range, 0.1–168 months). Only 2 patients in this subgroup survived longer than 2 years from diagnosis. The comparison of the baseline clinical data between deceased and alive patients with IHES showed that the former group was significantly older at diagnosis and had a higher leukocyte count and blood and marrow eosinophilia. Details are shown in TABLE 1.

All but 1 deceased patient had impairment of 2 or more organs at diagnosis. The involvement of the following organs was observed: heart (n = 7; 78%), lungs (n = 3; 33%), spleen (n = 2; 22%), liver (n = 4; 44%), lymph nodes (n = 2; 22%), and central nervous system (n = 1; 11%). Seven of nine deceased patients with IHES (78%) had at least 1 blood abnormality except eosinophilia at diagnosis: anemia (n = 3), thrombocytopenia (n = 4), and thrombocytosis (n = 3). All but 2 patients were receiving cardiac medications including β-blockers, diuretics, and angiotensin-converting enzyme inhibitors. Patients who died from cerebral complications had no abnormalities in coagulation tests. In total, all 9 patients were treated with prednisone (PDN) as the first-line treatment for IHES. The starting PDN dose varied from 0.5 mg/kg to 1 mg/kg. Three patients received PDN as monotherapy, and two of them died within 1 month from the start of therapy. Due to insufficient response to PDN, the remaining patients received other treatments: hydroxyurea (n = 6), imatinib (n = 5), interferon α (n = 2), cytarabine (n = 2), mercaptopurine (n = 1), and busulphan (n = 1).

None of the patients with poor outcome achieved a stable and long-term response to treatment. The causes of death were found to be cardiac-related in 6 patients, whereas 3 patients died of vascular complications within the central nervous system. Cardiovascular risk factors were present in 5 of 9 deceased patients. No patient was heavy smoker or obese. Dyslipidemia was not detected. Angiotensin-converting enzyme inhibitors were given for mild hypertension in 4 patients (patients No. 4, 5, 6, 7), while 2 patients (patients No. 6 and 7) received an oral hypoglycemic agent (metformin) for diabetes. A postmortem examination was consistent with the clinical diagnosis in all 4 autopsied patients. A summary of patients with fatal outcome is presented in Supplementary material online (*Table S1*).

The following variables were found to affect the overall survival in the univariate analysis: age, cardiac involvement, leukocyte count, and blood and marrow eosinophilia. Only marrow eosinophilia exceeding the median value (37%) was found to be an adverse prognostic factor in the multivariate model (hazard ratio, 14.6; 95% confidence interval, 1.44–149.2; $P = 0.02$). Data are shown in Supplementary material online (*Table S2*). No correlations were found between blood and marrow eosinophilia and cardiac involvement ($r = 0.13$, $P = 0.4$ and $r = 0.31$, $P = 0.06$, respectively).

Discussion Recent years have brought a significant improvement in diagnostic methods and therapeutic approach in patients with HES. This is especially true for a subset of HES patients with a detectable F/P transcript. The use of imatinib for F/P-positive HES has allowed to achieve complete hematologic and molecular responses in nearly 100% of treated patients.[5] For nonmolecularly defined HES, corticosteroids remain the first-line choice.[1] All available reports on survival rates in HES did not include patients with a known PDGFRA mutation status. In our study, deaths were seen only in patients with IHES, whereas no fatal outcomes occurred in patients with HES F/P+.

Survival in patients with HES has improved over the years but cardiac dysfunction remains the most frequent cause of death. However, only a few studies on mortality in HES have been published so far. The first analysis was from the 1970s and included 57 patients with HES, where 65% of deaths were due to cardiac failure with an overall survival of only 12% at 3 years.[6] Cardiac involvement, features of myeloproliferation, resistance

to steroids, male sex, and height of eosinophilia were predictors of poor outcome in the study of Lefebvre et al.[7] The overall survival rates were 80% at 5 years and 42% at 10 and 15 years. However, no patient had the F/P fusion transcript.

A recent retrospective study reported on mortality in 247 patients with HES who were followed up for 19 years. The cause of death was identified for 15 of 23 deceased patients (10%). Cardiac dysfunction remained the main cause of fatal outcome and was reported for 33% of the cases. The remaining causes of death included infections, unrelated malignancies, and thrombotic and vascular complications. However, this large analysis should be treated with caution. A molecular study for the presence of F/P rearrangement was performed only in 4 of the 23 deceased patients, and peak blood eosinophilia was available for a minority of subjects who died. In some cases, organ involvement was based on a clinical examination, and autopsy reports were not available.[4] In contrast, our study included patients with a strictly defined IHES population. Our survival rates were quite similar to those of the French study on patients with HES: the 5-year, 10-year, and 15-year survival rates were 100%, 87%, and 66%, respectively.[8] The causes of death were cardiovascular and were secondary to HES in all our patients.

Unexpectedly, blood eosinophilia at diagnosis was unrelated to death in the Cox regression model. Of note, no studies have reported a correlation between the level of HE and organ damage. Two patients had cerebral bleeding, which remains a rare HES manifestation. It seems that the substances released from eosinophilic granules may impair coagulation, resulting in clotting disturbances.[9]

Despite the current progress, factors that may contribute to the aggressive nature of HES remain unknown. The development of eosinophilia-related organ damage remains unpredictable, and the presence of "benign" and "aggressive" forms of eosinophils cannot be excluded.[10] Many patients may have severe HE without organ impairment despite the lack of eosinophilia-lowering treatment.[11] In contrast, some patients with a short history of moderate HE developed irreversible organ damage.

Due to the rarity of HES in the general population, it seems crucial to educate doctors of different specialties about the need for a regular blood count. Otherwise unexplained cardiovascular manifestations along with persistent blood eosinophilia should prompt doctors to consider a rapid diagnostic workup for HES. A close monitoring and early treatment may improve survival in some patients.

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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