

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

## Molecular Diagnostics and Treatment of Patients with the Hypereosinophilic Syndrome

Marc E. Rothenberg MD, PhD  
 Director, Division of Allergy and Immunology  
 Director, Cincinnati Center for  
 Eosinophilic Disorders  
 Professor of Pediatrics  
 Cincinnati Children's Hospital Medical Center  
 University of Cincinnati College of Medicine  
 Cincinnati, Ohio

**H&O** Could you describe the manifestations and pathophysiology of hypereosinophilic syndrome (HES)?

**MR** Hypereosinophilic syndrome (HES) is composed of a group of heterogeneous disorders that were classified in a review published several years ago<sup>1</sup>; each different form of HES has a distinct pathogenesis. The ensuing discussion concerns HES, which is best categorized by the myeloproliferative and the lymphoproliferative variants.

The myeloproliferative variant is the more aggressive form of HES that is associated with features of myeloproliferative disorders. It is characterized by known chromosomal events, particularly a fusion event that activates the tyrosine kinase platelet-derived growth factor receptor alpha (PDGFRA); this is a unique fusion with an interstitial deletion in chromosome 4 (del[4q12]), which results in the formation of a fusion gene between an uncharacterized gene Fip1-like 1 and the PDGFRA gene (FIP1L1-PDGFRA). The World Health Organization (WHO) has classified this form of HES as a chronic eosinophilic leukemia.

The lymphoproliferative variant is associated with clonal populations of abnormal, activated T lymphocytes, constituting a secondary eosinophilia from an abnormal lymphocyte population, often involving a clonal expansion.

**H&O** What are the genetic factors that confer risk for HES?

**MR** The only genetic irregularity in HES that has been clearly documented is the FIP1L1-PDGFRA. Genes that fuse to PDGFRA trigger constitutively activated tyrosine kinases, which drive clonal cell proliferation.

**H&O** What is the standard-of-care therapy for HES?

**MR** First, the most important issue in the management of HES is to rule out all other known causes of hypereosinophilia—primarily infection, drug-induced and systemic disorders such as vasculitis, and solid-organ tumors. After these have been ruled out, as well as the possibility of the myeloproliferative variant of HES (for which imatinib [Gleevec, Novartis] is first-line therapy), the standard of care is the long-term use of systemic corticoids such as corticosteroids, prednisone, and prednisolone, to which most patients are responsive. The patient inevitably becomes steroid-dependent, in which case steroid-sparing agents such as hydroxyurea and vincristine are required.

Additional therapy for HES that is independent of steroids are interferon alpha and alemtuzumab (Campath, Bayer Healthcare), which is an anti-CD52 antibody that has been shown in the last several years to be effective as well. HES is amenable to bone mar-

row transplant, and there have been a number of these patients reported in the literature. Also, even if a patient is FIP1L1-PDGFR $\alpha$ -negative, a trial of imatinib may be warranted because people without this fusion gene will sometimes still be responsive.

Finally, anti-interleukin (IL)5 is a drug that is effective but is not yet approved by the US Food and Drug Administration (FDA). It has been shown to be effective in lowering eosinophils and steroid doses as well as being well-tolerated and safe.

It is important to realize that HES is a life-threatening disorder with a significant morbidity and mortality rate. Patients need to be avidly monitored. As the heart is one of the primary organ systems affected, regular echocardiograms and high vigilance monitoring for vasculopathy, hypercoagulation, and thrombosis are key. The physician also needs to monitor for steroid side effects. For confirmed HES patients, keeping the eosinophil levels low is crucial, and medication should be adjusted accordingly. Serum eosinophil levels should be kept under 500, and in some patients under 200 per microliter.

Corticosteroid toxicities are wide-ranging and include hyperglycemia, mood changes, hypertension, atherosclerosis, cataracts, or skin atrophy. Almost every organ can be affected, and side effects are dependent on the individual and the dose. Imatinib is associated with cardiac, liver, and gastrointestinal toxicity, but is generally very well-tolerated compared to chemotherapy.

### **H&O** How is IL5 involved in HES pathogenesis and how can it play a part in potential treatment?

**MR** Among the many pathways of HES development, IL5 has been shown to be an eosinophil growth factor that regulates eosinophil mobilization from the bone marrow and an activating and survival factor. Neutralizing IL5 would thereby block multiple steps in the pathway and dramatically lower eosinophil levels in the blood.

In a study published in the *New England Journal of Medicine*,<sup>2</sup> Rothenberg and associates focused on the effect of mepolizumab, an anti-IL5 monoclonal immuno-

globulin G1 antibody. By binding to IL5, mepolizumab prevents it from linking with receptors on the surface of eosinophils. As preliminary studies had shown, mepolizumab had few side effects and effectively lowered eosinophil levels; this study aimed to evaluate the corticosteroid-sparing effects of mepolizumab in patients with HES. Patients were FIP1L1-PDGFR $\alpha$ -negative and received either intravenous mepolizumab or placebo while their regular prednisone dose (20–60 mg per day) was tapered.

The primary end point—prednisone dose to 10 mg or less per day for 8 or more consecutive weeks—was reached in 84% of patients in the mepolizumab group, compared with 43% of patients in the placebo group (hazard ratio [HR], 2.90; 95% confidence interval [CI], 1.59–5.26;  $P < .001$ .); 95% of the mepolizumab group achieved a blood eosinophil count of less than 600/ $\mu$ L for 8 or more consecutive weeks, compared with 45% of the placebo group (HR, 3.53; 95% CI, 1.94–6.45;  $P < .001$ ). In this study, the key point was that the mean steroid dose needed for the mepolizumab group was lower than that for the placebo group.

Another noteworthy anti-IL5 antibody is reslizumab (Ception Therapeutics). The manufacturer is currently conducting a trial in eosinophilic esophagitis, which is a more common eosinophilic disorder.

### **H&O** What are the most important issues in the future research of HES?

**MR** The key to HES research is the determination of which tyrosine kinases are involved in these diseases and the development of other classes of drugs like imatinib. Anti-IL5 antibodies seems to be an effective medication; therefore, it is important to conduct the appropriate trials to secure FDA approval.

### **References**

1. Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hyper-eosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol*. 2006;117:1292-302.
2. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hyper-eosinophilic syndrome with mepolizumab. *N Engl J Med*. 2008;358:1215-1228.