A Critical Appraisal of Conventional and Investigational Drug Therapy in Patients With Hypereosinophilic Syndrome and Clonal Eosinophilia

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Hypereosinophilic syndrome (HES) is a rare disorder characterized by persistent and marked eosinophilia, leading to end-organ damage. Over the last decade, great progress has been made in unraveling the molecular basis of HES that has resulted in the characterization of specific genetic alterations linked to clonal eosinophilia. The most frequently encountered genetic aberrancy is the cryptic FIP1-like 1/platelet-derived growth factor receptor α (FIP1L1-PDGFRA) fusion transcript, which results in an eosinophilic, myeloproliferative disorder. In addition, in a subset of patients with HES, a population of aberrant T cells that secretes interleukin-5 can be identified, indicating the existence of lymphocyte-mediated hypereosinophilia. These new insights have led to both a genetically based (re)classification of eosinophilic blood disorders and to effective therapies with targeted agents, such as small-molecule tyrosine kinase inhibitors (eg, imatinib, nilotinib, PKC412) and, more recently, monoclonal antibodies (eg, mepolizumab, alemtuzumab). These targeted therapies hold great promise for improving the clinical outcomes of patients with HES and clonal eosinophilia, and they have exhibited relatively safe toxicity profiles. ***Cancer* 2007;110:955–63.** © *2007 American Cancer Society.*

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Hypereosinophilic syndrome (HES) is a rare hematologic disorder characterized by the overproduction of eosinophils in the bone marrow, eosinophilia, tissue infiltration, and end-organ damage by eosinophil infiltration and secretion of mediators.[1] The diagnosis of HES is based on marked eosinophilia (absolute eosinophil count $>1.5 \times 10^9$/L), chronic course (>6 months), exclusion of other evident etiologies for eosinophilia (eg, parasitic infestations, allergic diseases, Hodgkin disease, and metastatic cancer), and signs and symptoms of eosinophil-mediated tissue injury (eg, cardiomyopathy, gastroenteritis, pneumonitis, cutaneous lesions, sinusitis, neurologic and ophtalmologic manifestations, and vasculitis).[2–5] Over the last few years, considerable insights with regard to the pathogenesis of HES have been gained that have highlighted the marked heterogeneity of patients with this disorder. A diagnosis of "true" HES, according to World Health Organization, is predicated on demonstrating the absence of any molecular or cytogenetic features of clonality or any bone marrow findings suggesting an abnormal population of mast cells, monocytosis, or evidence of trilineage myeloproliferation or dysplasia.[6,7] It is now clear that there are at least 3 distinct groups of patients among those who previously were diagnosed with "idio-

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pathic" HES. First, a subset of patients has been reclassified with "clonal" eosinophilia (chronic eosinophilic leukemia [CEL]) because of the identification of the Fip1-like 1/platelet-derived growth factor receptor α (FIP1L1-PDGFRA) fusion transcript.[8–11] These patients require a different therapeutic approach, which is addressed separately below. Second, there is a subset of patients with HES in which no evidence of clonality can be demonstrated with currently available techniques, and they still have disease that must be considered "idiopathic." However, it is well documented that patients with "idiopathic" HES who present without any distinct cytogenetic abnormalities may have disease that ultimately evolves into acute leukemia or aggressive forms of myeloproliferative disorders.[12,13] The disease in this group often is referred to as a myeloproliferative variant of HES. Finally, there is a third subset of patients that carries an abnormal T-cell population (helper Th2 lymphocytes), detectable either by flow cytometry or polymerase chain reaction analysis,[14–16] that produces interleukin-5 (IL-5), a cytokine required for the growth and differentiation of eosinophils.[17] These patients have disease that frequently is referred to as a lymphoproliferative variant of "idiopathic" HES. This likely incomplete division has had direct implications regarding treatment options for these patients. Hence, the distinction between clonal and idiopathic eosinophilia is not conspicuous in many instances, which does not necessarily suggest monoclonal proliferation of eosinophils in the HES but, rather, highlights the absence of such evidence.[18] Readers are referred to an excellent recent review of the pathophysiology of blood eosinophilia that includes a detailed summary of all new molecular discoveries; the current report should be considered a companion to that summary by Tefferi et al.,[19] because we focus on the treatment options for these patients.

Cytotoxic Therapy

Idiopathic HES

Numerous cytotoxic approaches have been used in the treatment of HES and still are considered frontline therapy for patients with FIP1L1-PDGFRA-negative disease. The first descriptions of HES were associated with a median survival of approximately 9 months. The main culprit for this grim outcome was end-organ damage because of tissue infiltration by eosinophils, chiefly leading to cardiovascular damage (congestive heart failure, endocarditis, atrioventricular valvular incompetence, thomboemboli) as the primary cause of death.[3] Therefore, the major objective of therapy for patients with HES has been aggressive debulking of the eosinophil burden in an attempt to prevent damage to vital organs. Prompt responses usually were observed in patients who received prednisone at a dose of 1 mg/kg daily. Unfortunately, some patients exhibited resistance to corticosteroids, and most developed recurrent disease during steroid tapering,[2,3] thus requiring additional therapy. Furthermore, long-term corticosteroid therapy has been associated with potentially serious side effects.

Oral hydroxyurea administered at an initial dose of 500 mg daily is highly effective in corticosteroid-resistant patients.[20] Anemia and thrombocytopenia are the main associated toxicities, but these may be managed with dose reductions or temporal hydroxyurea discontinuation.[2] A variety of other cytotoxic agents have been described anecdotally for the treatment of HES. Intravenous vincristine at doses from 1.5 mg to 2 mg at 2-week intervals has been beneficial in several patients.[21] Its main limitation is the development of neurotoxicity, which sometimes may be difficult to distinguish from the peripheral neuropathy associated with HES. Antimetabolites, such as 6-tioguanine,[22] 2-chlorodeoxyadenosine, cytarabine,[23] methotrexate, and colchicine,[24] reportedly had only a partial and transient effect on eosinophil counts. Etoposide was administered to 1 patient with HES and effectively controlled the symptoms, but treatment had to be terminated because of bone marrow suppression.[25] Alkylating agents, such as chlorambucil[2] and cyclophosphamide,[26] have produced acceptable long-term control of the disease in some patients.

FIP1L1-PDGFRA-positive CEL

Because of highly successful therapy with the tyrosine kinase inhibitor (TKI) imatinib mesylate, cytotoxic therapy may be considered as second-line therapy for patients with FIP1L1-PDGFRA-positive CEL in the event of resistance or intolerance to TKI treatment.

Immunosuppressant Agents

Idiopathic HES

An alternative approach to the treatment of HES is the employment of immunomodulatory/immunosuppressant agents. The rationale for the use of such an approach has been provided by the demonstration of a clonal and immunophenotypically aberrant T-cell population in a subset of patients with HES.[14–16] Thus, a second line of treatment in HES has been the administration of interferon-α, conventionally at a dose ranging from 1 million to 8 million units 3 times per week subcutaneously. Numerous reports have documented long-lasting improvements in the majority of patients who were treated in such fash-

ion[24,27,28] with control of symptoms and with significant decreases in eosinophil counts and eosinophil major protein levels.[29,30] Frequently, the initial dose needs to be tapered because of cytopenias, primarily thrombocytopenia. A wide array of side effects has been described with the use of interferon-α that frequently results in high drop-out rates. Occasionally, cessation of interferon-α has been linked to rebound eosinophilia.[31,32] Cyclosporine A also has been used in the treatment of HES. An oral dose of 6 mg/kg daily reportedly was effective for controlling HES-related symptoms.[33,34] The use of azathioprine has been described in several case reports as effective for controlling symptoms in patients with HES, likely reflecting the immunologic nature of some types of HES.[35–37]

FIP1L1-PDGFRA-positive CEL

With the availability of TKIs and cytotoxic medications, the immunomodulatory/immunosuppressant agents have little role in the therapy for patients with FIP1L1-PDGFRA-positive CEL.

Allogeneic Stem Cell Transplantation

Idiopathic HES

The first described case of allogeneic stem cell transplantation (allo-SCT) in a patient with HES who had only had a transient response to conventional treatment with corticosteroids and hydroxyurea was reported in 1988. This patient had a full hematologic recovery but died within 3 months after transplantation because of diffuse cytomegalovirus infection.[38] Subsequent reports of successful allo-SCT have disclosed significant rates of complete remission from 8 months to 40 months after transplantation using either bone marrow[39,40] or peripheral blood[41,42] as the source of stem cells. A nonmyeloablative allo-SCT after a reduced-intensity preparative regimen of melphalan and fludarabine reportedly induced a complete remission that lasted longer than 10 months in 2 patients with HES.[43] In both patients, complete donor chimerism was achieved, providing proof of principle for the feasibility of nonmyeloablative allo-SCT for patients with HES, who can develop important comorbidity secondary to organ eosinophilic infiltration. Currently, allo-SCT still is considered an investigational modality for patients with HES and should be recommended only to those patients who do not respond or who have primary disease that is resistant to cytotoxic and immunosuppressant therapy.

FIP1L1-PDGFRA-positive CEL

Recently, it was reported that the FIP1L1-PDGFRA fusion transcript could be eradicated completely after allo-SCT.[44] However, because imatinib therapy has been proven effective in eradicating the disease in the great majority of patients with FIP1L1-PDGFRA-positive CEL, and because patients who are resistant or intolerant to imatinib most likely can be salvaged with newer TKIs and cytotoxic medications, allo-SCT should be considered "the last resort" approach for these patients.

TKIs

The use of TKIs as therapy for patients with HES is related closely to the discovery of the FIP1L1-PDGFRA oncogene in responding patients. This set the stage for a revision of the World Health Organization diagnostic criteria for HES and led to the reclassification of FIP1L1-PDGFRA-positive disease as CEL. Therefore, below, the use of TKIs in these patients is described first.

FIP1L1-PDGFRA-positive CEL

Imatinib mesylate. Imatinib selectively inhibits a series of protein tyrosine kinases, including Bcr-Abl, Kit, PDGFRA, and platelet-derived growth factor receptor β (PDGFRB), among others. The activity of this TKI against Bcr-Abl-positive cell lines was described first in 1996[45] and was followed readily by further studies translating this activity into the clinical arena, which led to the rapid approval of imatinib for the treatment of chronic myelogenous leukemia (CML).[46–49] Before the discovery of the FIP1L1-PDGFRA fusion oncogene, it had been documented in several reports that empiric therapy with imatinib induced rapid and dramatic complete hematologic remission in patients with HES at doses ranging between 75 mg and 400 mg daily.[26,50–52] Gleich et al. reported on 5 patients who received imatinib at a dose of 100 mg daily. It is interesting to note that, in that study, 4 men who had normal serum IL-5 concentrations achieved complete hematologic responses, whereas a woman who had an increased serum IL-5 concentration failed to respond. All patients who responded stopped other treatments and reduced imatinib mesylate to a dose of 200 mg per week. The exact mechanism by which imatinib exerted such a powerful effect in patients with HES was unknown at that time but suggested the possibility of the presence of an activated kinase, such as Abl, PDGFR, or kit receptor tyrosine kinase (KIT), all of which are targets of imatinib.[51] Cools et al. identified an interstitial deletion on chromosome 4q12, which was undetectable by conventional cytogenetic techniques, that resulted in the fusion FIP1L1-PDGFRA kinase in 9 of 16 patients with HES and in 5 of 9 patients who achieved durable responses to imatinib.[1] In vitro, imatinib mesylate inhibited the constitutively

active FIP1L1-PDGFRA tyrosine kinase with a 50% inhibitory concentration (IC_{50}) value of 3.2 nM, significantly lower than the value obtained in Bcr-Abl-expressing cell lines (>250 mM),[1,53] further supporting the clinical efficacy of this TKI in patients who harbor the transcript.[1] These results also were confirmed in the EOL-1 cell line, which was derived from a patient with FIP1L1-PDGFRA-positive leukemia.[54] It is noteworthy that the FIP1L1-PDGFRA transcript can be detected in early hematopoietic progenitors and, in rare instances, in systemic mastocytosis associated with eosinophilia[55,56]; and the presence of the FIP1L1-PDGFRA fusion kinase usually is associated with elevated serum levels of tryptase and vitamin B12.[57,58]

The clinical activity of imatinib in the treatment of patients with CEL has been confirmed in multiple reports,[59–62] and there is general consensus regarding the use of imatinib as first-line therapy in patients who express FIP1L1-PDGFRA. The incidence of FIP1L1-PDGFRA-positive patients with eosinophilia, however, is not high. Although it was reported initially in 9 of 16 patients who were tested, a more recent analysis of the presence of FIP1L1-PDGFRA in samples from much larger groups of patients with eosinophilia suggested that its incidence was as low as 4%.[63]

Despite its impressive activity in patients with FIP1L1-PDGFRA-positive CEL, imatinib therapy has been associated with important side effects, including oligospermia and, more important, cardiac events.[64,65] In fact, several reports of acute imatinib-induced left heart failure have been reported during the first 14 days of therapy with imatinib.[65] Patients with potential cardiac involvement can be identified before the start of imatinib by echocardiography and determination of serum troponin levels. The presence of elevated levels of troponin T before and right after the onset of imatinib therapy accurately predicts the development of acute left ventricular dysfunction.[65] In these instances, pretreatment with systemic corticosteroids is highly recommended.[65]

Paralleling the experience in patients with CML, imatinib resistance also has been observed in patients with CEL who were treated with this TKI. The FIP1L1-PDGFRA T674I mutant isoform is homologous to BCR-ABL T315I in CML and confers remarkable resistance to imatinib. To our knowledge to date, only 2 cases of CEL with acquired imatinib resistance have been reported.[1,51] In both patients, a T674I mutation in the adenosine triphosphate (ATP)-binding domain of PDGFRA was identified. Other alternative mechanisms linked to imatinib resistance have been described in CML, including Bcr-Abl overexpression, extracellular sequestration of imatinib by α-1-acid glycoprotein, and an enhanced active imatinib efflux by transmembrane pump proteins, such as multidrug resistance/p-glycoprotein.[66,67] These mechanisms also are likely to be encountered in patients with FIP1L1-PDGFRA-positive CEL.

Increasing concerns regarding the development of clinical resistance to imatinib, along with the finding that severe side effects have been observed in some patients during imatinib therapy, have paved the way for the investigation of novel molecules with augmented potency and favorable toxicity profiles.[68–70] Research involving other small-molecule TKIs has yielded several compounds with excellent pharmacokinetic profile and high efficacy as inhibitors of the FIP1L1-PDGFRA kinase.

Nilotinib. Nilotinib (AMN107) is an aminopyrimidine derivative that was designed rationally based on the crystallographic structure of the imatinib-Bcr-Abl complex.[70] The replacement of the N-methylpiperazine ring in the imatinib molecule has led to a compound that, similar to imatinib, is a competitive inhibitor at the ATP-binding site of Bcr-Abl.[71] It has been demonstrated that nilotinib is from 20-fold to 30-fold more potent than imatinib as an Abl inhibitor in imatinib-sensitive CML cell lines and from 3-fold to 7-fold more potent in imatinib-resistant cell lines.[71,72] Nilotinib has excellent pharmacokinetic and safety profiles,[71,73–75] and it has demonstrated activity in clinical trials involving patients with disease that was CML resistant or intolerant to imatinib.[76] The activity of nilotinib against other kinases, such as KIT, PDGFRA, and PDGFRB, has been investigated.[76] The ranking of nilotinib activity against these kinases is different for nilotinib (Bcr-Abl> PDGFR>KIT) compared with imatinib (PDGFR> KIT>Bcr-Abl).[77] It has been demonstrated that nilotinib inhibits cell proliferation driven by PDGFRA and PDGFRB in vitro and is effective in controlling myeloproliferative disease caused by TEL-PDGFRB and FIP1L1-PDGFRA in murine bone marrow transplantation models. However, there are somewhat conflicting reports regarding the activity of nilotinib against the PDGFRA T674I mutant kinase. Initial reports suggested that nilotinib was able to overcome the resistance conferred by the imatinib resistant point mutation T681I but had no activity against the PDGFRA T674I mutated kinase.[75,76] However, recent reports have indicated that nilotinib is capable of suppressing the growth of Ba/F3 cells transfected with FIP1L1-PDGFRA T674I with an IC_{50} of 376 nM.[78] These results indicated that therapy with nilotinib may override imatinib resistance conferred by FIP1L1-PDGFRA T674I kinase.

Dasatinib. Dasatinib (BMS-354825) is an oral, multitargeted kinase inhibitor with potent activity against the Bcr-Abl (IC_{50}, <1 nM), KIT (IC_{50}, 13 nM), PDGFRB (IC_{50}, 28 nM), and epithelial cell kinase A2 (IC_{50}, 17 nM) receptor kinases, among others.[62,79–81] Dasatinib is approximately 300-fold more potent against Bcr-Abl than imatinib and is active against all tested Abl mutant isoforms except for T315I. Dasatinib has demonstrated high efficacy in Phase I and II studies in patients with CML or with Bcr-Abl-positive acute lymphoblastic leukemia after failure on imatinib therapy.[82] The clinical activity of dasatinib in patients with CML and its potent activity against PDGFR provide the foundation for its possible use in patients with FIP1L1-PDGFRA-positive CEL who are resistant or intolerant to imatinib.

Sorafenib. Sorafenib (BAY 43-9006) initially was identified in 2001 as a potent B-RAF and vascular endothelial growth factor receptor (VEGFR) inhibitor and, subsequently, demonstrated the ability to inhibit the fms-related tyrosine kinase 3 (FLT3), KIT, and PDGFR tyrosine kinases.[83] Sorafenib recently was approved for the treatment of advanced renal cell carcinoma[84] and currently is being tested in clinical trials for the treatment of a variety of solid tumors, including pancreatic cancer.[85–87] Results from these studies have demonstrated that steady-state concentrations of up to 4 μM are safely achievable in patients with a dose of 100 mg daily.[86] It was reported recently that sorafenib inhibited the proliferation of FIP1L1-PDGFRA- and FIP1L1-PDGFRA T674I-transformed Ba/F3 cells with IC_{50} values of 4 nM and 54 nM, respectively. In addition, sorafenib induced apoptosis of the EOL-1 cell line at a low nanomolar concentration (IC_{50}, 0.5 nM). Western blot analysis confirmed that sorafenib directly inhibited the phosphorylation of FIP1L1-PDGFRA, FIP1L1-PDGFRA T674I, and extracellular signal-regulated kinase 1/2 (ERK1/2). Overall, these data suggest that sorafenib is another promising candidate for the treatment of FIP1L1-PDGFRA-positive patients to overcome imatinib resistance associated with the expression of FIP1L1-PDGFRA T674I.[88,89]

PKC412. PKC412 is a staurosporine derivative that originally was identified as an inhibitor of protein kinase C (PKC), but it subsequently demonstrated the ability to inhibit other kinases, including VEGFR, FLT3, KIT, kinase insert domain receptor, and PDGFR.[90] PKC412 has demonstrated broad antiproliferative activity against various tumors and normal cell lines in vitro[91]: It enhances sensitivity to radiation, and it potentiates the in vivo antitumor activity of some cytotoxic agents, such as doxorubicin.[92] Phase I studies have demonstrated that PKC412 has a good pharmacokinetic profile after oral administration,[93] and Phase II clinical trials have demonstrated that it has clinical activity in patients with acute myelogenous leukemia who have blasts with an activating mutation of FLT3, suggesting its potential use in combination with other chemotherapeutic agents.[94,95]

PKC412 inhibited the growth of FIP1L1-PDGFRA-expressing Ba/F3 cells with a cellular IC_{50} of approximately 130 nM.[96] However, Ba/F3 cells that were transformed with FIP1L1-PDGFRA N659D were not inhibited at concentrations of PKC412 as high as 400 nM.[94] It is noteworthy that PKC412 inhibited the proliferation of Ba/F3 cells that were transformed by FIP1L1-PDGFRA harboring the T674I mutation with an IC_{50} of approximately 100 nM.[94] The efficacy of PKC412 also was evaluated in a murine bone marrow transplantation model of FIP1L1-PDGFRA-induced myeloproliferative disease. Recipient mice were divided into 3 groups that received treatment with imatinib, PKC412, or placebo, respectively. Mice that were treated with imatinib and transplanted with bone marrow cells expressing the FIP1L1-PDGFRA T674I imatinib-resistant mutation developed disease with the same penetrance as the placebo-treated mice. However, administration of PKC412 to animals with myeloproliferative disease induced by the FIP1L1-PDGFRA T674I transcript led to significant prolongation of survival and reductions of leukocyte counts and spleen weight compared with placebo-treated animals. These data suggest that PKC412 may represent a molecularly targeted therapy for CEL and other diseases that express activated PDGFRA regardless of the presence of the imatinib-resistant T674I mutation.[94]

Idiopathic HES

Imatinib therapy is not recommended initially for patients with FIP1L1-PDGFRA-negative HES. However, a trial of imatinib therapy may be justified in these patients when they become refractory to conventional cytotoxic or immunomodulatory/immunosuppressant therapy, because a fraction of these patients can respond to imatinib.[1] Further investigations are warranted to define the molecular basis of imatinib response in patients with FIP1L1-PDGFRA-negative HES.[97] This may be explained, for example, by the existence of FIP1L1-PDGFRA fusion transcripts with different breakpoints within the *FIP1L1* gene, the presence of fusion transcripts involving a gene adjacent to FIP1L1 that could partner with PDGFRA, the fusion of the KIT gene with PDGFRA, or the presence of a yet to be discovered fusion kinase amenable to inhibition by imatinib.[1]

Other newer TKIs are being evaluated in clinical trials for patients wit HES. Although preclinical studies of these medications have been conducted in PDGFR-expressing models, as described above, the number of FIP1L1-PDGFRA-expressing patients with resistance to imatinib is extremely low, and this group is not amenable to the conduct of clinical studies. Because several other tyrosine kinases (eg, KIT) may be involved in the pathophysiology of HES and may be affected by newer TKIs, it is reasonable to study them in patients with "idiopathic" HES that does not respond to standard therapies. Data on 11 patients with HES who were treated with nilotinib 400 mg twice daily in a Phase II trial recently were reported.[98] Although nilotinib therapy, in general, was well tolerated, only 1 patient (9%) achieved a complete response, whereas 5 other patients (45%) had stable disease. Dasatinib is another new TKI that currently is being evaluated in patients with "idiopathic" HES.

Monoclonal Antibodies

Idiopathic HES

Anti-IL-5 monoclonal antibodies. IL-5 is a major cytokine that is involved selectively in the maturation, activation, and proliferation of eosinophils, and elevated levels of IL-5 are encountered commonly in patients with HES.[99] IL-5 is produced mainly by Th2 lymphocytes, mast cells, and eosinophils; therefore, it represents a potential target for the treatment of HES.[15] Two humanized monoclonal antibodies (MoAbs) against IL-5 have been used in clinical trials involving patients with eosinophil diseases, SB-240563 or mepolizumab, a humanized mouse MoAb,[100] and SCH 55700, a humanized rat MoAb.[101] These antibodies were developed initially for the treatment of bronchial asthma in humans, although, unfortunately, the initial results in that setting were disappointing.[102] Administration of mepolizumab to patients with asthma significantly lowered peripheral blood and sputum eosinophil counts, but it did not have an effect on the airway hyperresponsiveness or on the allergen-induced, late asthmatic response, despite reducing lung eosinophil levels by 55%.[103,104]

What to our knowledge is the first case report of mepolizumab therapy in a patient with HES was published in 2003.[105] Mepolizumab administered at a dose of 750 mg 3 times per week effectively reduced serum IL-5 levels and peripheral blood eosinophil counts and markedly relieved the HES-related symptoms. However, this response was transient and was followed by rebound eosinophilia within days after the last administration of the MoAb.[105] These results were confirmed later in a pilot study that involved 3 patients who had HES and eosinophilic dermatitis and who experienced rapid relief of skin symptoms and pruritus and normalization of blood eosinophil counts within 24 hours of intravenous administration of mepolizumab.[106] Results from an international, multicenter, randomized, double-blind, placebo-controlled trial of mepolizumab in patients with HES recently have been reported.[107] In total, 85 patients with FIP1L1-PDGFRA-negative HES who received from 20 mg to 60 mg daily of prednisone monotherapy to maintain a blood eosinophil count $<1 \times 10^9$/L were enrolled. Patients were randomized to receive intravenous mepolizumab 750 mg (n = 43 patients) or saline (n = 42 patients) every 4 weeks for 36 weeks. Prednisone was tapered at weekly intervals after the first infusion according to blood eosinophil counts and clinical criteria. Overall, 84% of patients on the mepolizumab arm achieved the primary endpoint of decreasing the prednisone requirements below 10 mg daily for at least 8 consecutive weeks, compared with 43% of patients who were randomized to the placebo arm ($P < .001$). The time required to achieve this endpoint was significantly shorter in the mepolizumab arm than in the placebo arm ($P = .002$). In addition, more patients who were randomized to receive mepolizumab achieved an eosinophil count $<0.6 \times 10^9$/L for at least 8 consecutive weeks (95% vs 45%; $P < .001$; 95% confidence interval, 4.74–75.17%). These findings indicate that mepolizumab holds promise because of its lack of serious side effects and its effectiveness in patients with "idiopathic" HES.

Anti-CD52 MoAbs. Alemtuzumab (CAMPATH) is an MoAb that targets the CD52 surface protein that is expressed on the surface of human eosinophils. Blockade of CD52 by mouse anti-CD52 MoAb (immunoglobulin G3 [IgG3]) and humanized anti-CD52 MoAb (IgG1) with goat-antimouse antibody and mouse-antihuman antibody, respectively, resulted in dose-dependent inhibition of reactive oxygen species production of eosinophils after stimulation with C5a, platelet-activating factor, and granulocyte-macrophage–colony-stimulating factor.[108] Thus, CD52 blockade may be relevant clinically by reducing the deleterious effects of human eosinophils in the inflammatory tissue. The initial evidence of the activity of alemtuzumab in HES was provided by 2 case reports of patients who were refractory to imatinib and nonmyeloablative allogeneic peripheral blood SCT.[109,110] More recently, a pilot trial of alemtuzumab in 9 patients with FIP1L1-PDGFRA-negative HES was reported.[111] Alemtuzumab was administered in weekly cycles at a dose of 30 mg (8 patients) or 10 mg (1 patient) 3 times per week either intravenously or subcutaneously. The median absolute eosinophil count

was 9×10^9/L (range, 0.7–30×10^9/L). Patients had received a median of 3 prior therapies (range, 2–6 prior therapies), including prednisone (n = 9 patients), imatinib (n = 7 patients), dasatinib (n = 3 patients), interferon-α (n = 3 patients), nilotinib (n = 2 patients), and cladribine (n = 2 patients). A complete normalization of the peripheral blood eosinophil count was observed in 8 patients (89%) within 4 weeks of therapy and was undetectable in 6 of them. However, 5 patients who were withdrawn from alemtuzumab therapy developed recurrent disease after a median of 3.5 weeks (range, 1–10 weeks), and 1 patient developed recurrent disease while receiving alemtuzumab after 14 weekly cycles. Three patients remain on alemtuzumab treatment; 2 are receiving 30 mg weekly as maintenance while they remain in complete hematologic response after ≥8 weeks and ≥19 weeks, respectively; and 1 patient with a partial response is receiving 30 mg 3 times per week. One patient who developed recurrent disease was rechallenged with alemtuzumab and, once again, achieved a normalized eosinophil count. Alemtuzumab generally was well tolerated, and only 2 patients experienced cytomegalovirus reactivation. These data underscore the remarkable activity of alemtuzumab in patients with FIP1L1-PDGFRA-negative HES. These results warrant further confirmation in larger clinical trials.

FIP1L1-PDGFRA-positive CEL

Because of the remarkable activity of imatinib in these patients and the availability of other standard therapies, MoAbs currently have no role as therapies for patients with FIP1L1-PDGFRA-positive CEL.

Conclusions

Recent advances in the pathogenesis of HES/CEL have facilitated the development of more effective drugs for patients with these myeloproliferative disorders. In this regard, the FIP1L1-PDGFRA fusion kinase has become an appealing target after its description in a subset of patients. This kinase is amenable to inhibition with small-molecule TKIs, such as imatinib and nilotinib. An important aspect of therapy with these agents is the development of resistance, which has been associated with the presence of the FIP1L1-PDGFRA T674 mutant isoform. This mutation is homologous to the T315I mutation occurring in the kinase domain of the Bcr-Abl tyrosine kinase, which confers insensitivity to imatinib, nilotinib, and dasatinib in patients with CML. Fortunately, alternative approaches, such as novel TKIs (eg, PKC412, sorafenib) or MoAbs against IL-5 (mepolizumab) or CD52 (alemtuzumab), may prove effective in this setting.

For the great majority of patients who are negative for the FIP1L1-PDGFRA fusion kinase, those with "idiopathic" HES, aside from the standard therapies with corticosteroids, hydroxyurea, and interferon-α, MoAb therapy (mepolizumab and alemtuzumab) appears to be a major new therapeutic approach; however, the hope is that the current intensive search for new molecular abnormalities in this disease will reveal potential targets for the development of novel targeted therapies. Finally, for patients who have disease that is resistant to medical therapy, allo-SCT may be a curative option.

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