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CLINICAL OBSERVATIONS

Comment on Pardanani et al, page 3038

The FIP1L1-PDGFRA syndrome: a case of mistaken identity?

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The diagnosis of hypereosinophilic syndrome (HES) has been largely a process of exclusion and by definition therefore, unsatisfactory. Frustrated hematologists were comforted by the knowledge that a better understanding of the molecular pathogenesis would eventually resolve their difficulties. This better understanding is now beginning to emerge.

Cools et al provided at least part of the explanation with the identification of the *FIP1L1-PDGFRA* fusion gene in a substantial proportion of cases.[1] The clinical significance of this observation is the prompt and remarkable response of such patients to imatinib. In the past year a number of groups have attempted to further classify the syndrome using associated clinical and pathologic features in fusion-positive patients. Klion et al were able to identify features that separated 9 of 15 cases of HES and were associated with the presence of the fusion gene and/or response to imatinib.[2] A prominent feature was a moderately raised serum tryptase, leading them to adopt the terminology HES-tryptase. Subsequently, Pardanani et al challenged this view on the basis of their observations of 5 patients thought to have systemic mast cell disease (SMCD), which suggested that *FIP1L1-PDGFRA* was more likely to be found in SMCD associated with eosinophilia (SMCD-eos).[3]

In this issue of *Blood*, Pardanani and colleagues provide important new information on the prevalence and characteristics of the *FIP1L1-PDGFRA* syndrome. They extended their observations to 57 patients with HES and 19 with SMCD-eos. Of the 11 patients positive for *FIP1L1-PDGFRA*, 10 had increased numbers of mast cells. The search criteria ensured that all study patients had eosinophilia, and whether there are patients with this fusion gene who do not have eosinophilia remains to be established. The authors considered that these 10 patients met the WHO criteria for SMCD[4] and proposed that they should form a subgroup, namely SMCD-eos. So is this the end of the story? Were the original diagnoses of HES incorrect? Well, the devil may be in the detail. In fact, 7 of the 10 fusion-positive patients were originally diagnosed as HES and only after the fusion gene was detected were they reviewed and reclassified as SMCD-eos. It is not clear, however, that the 57 patients with HES were subjected to the same level of scrutiny, so some doubt must remain as to whether similar patterns of macrocytosis can be present without the fusion gene.

So, is the *FIP1L1-PDGFRA* syndrome SMCD or HES or chronic eosinophilic leukemia (CEL)? Although an interesting intellectual argument, it may have little relevance. Within the context of the WHO classification of chronic myeloproliferative disorders, patients positive for *FIP1L1-PDGFRA* would be classified as chronic eosinophilic leukemia (CEL) rather than HES (see figure).[4] If *FIP1L1-PDGFRA* positivity were always associated with a diffuse mast cell infiltrate and a moderately raised serum tryptase, then further clarification regarding malignant mast cell involvement must come from the identification of the fusion gene in these cells. Rewriting the WHO classification now may be premature, but in all likelihood, the *FIP1L1-PDGFRA* fusion may simply define a separate entity of the myeloproliferative disorders.

The take-home message must be that all patients with persistent eosinophilia must be investigated thoroughly for all other reactive and clonal causes of eosinophilia, and such tests should include histochemical staining for mast-cell tryptase and serum tryptase levels, studies for c-kit mutations, and, of course, a search for the *FIP1L1-PDGFRA* fusion gene. In this respect, it is worth noting that the current reverse transcriptase–polymerase chain reaction (RT-PCR) test may lack some sensitivity, and, if negative, should always be followed by fluorescence in situ hybridization (FISH) and nested PCR analyses (European

Required: Persistent eosinophilia with eosinophil counts of at least 1.5 x 10^9/L in blood, increased numbers of bone marrow eosinophils, and myeloblasts less than 20% in blood or marrow.
1. Exclude all causes of reactive eosinophilia secondary to allergy, parasitic diseases, infectious diseases, pulmonary diseases (hypersensitivity pneumonitis, Loeffler, etc), and collagen vascular diseases.
2. Exclude all neoplastic disorders with secondary, reactive eosinophilia, such as T-cell lymphomas, Hodgkin disease, acute lymphoblastic leukemia/lymphoma, and mastocytosis.
3. Exclude other neoplastic disorders in which eosinophils are part of the neoplastic clone such as Ph-positive CML, AML including those with inv(16), t(16;16), and (p13;q22), other myeloproliferative diseases (PV, ET, CIMF), and myelodysplastic syndromes.
4. Exclude T-cell population with aberrant phenotype and abnormal cytokine production.
5. If there is no demonstrable disease that could cause the eosinophilia, no abnormal T-cell population, and no evidence of a clonal myeloid disorder, diagnose HES.
6. If all of the requirements, including conditions 1 to 4, have been met, and if the myeloid cells demonstrate a clonal chromosomal abnormality or are shown to be clonal by other means, or if blast cells are present in the peripheral blood (> 2%) or are increased in bone marrow (> 5% but < 19% of nucleated bone marrow cells), diagnose CEL.

Diagnosis of chronic eosinophilic leukemia and hypereosinophilic syndrome. Table was adapted with permission from Jaffe et al.[4] Ph indicates Philadelphia chromosome; CML, chronic myelogenous leukemia; AML, acute myeloid leukemia; PV, polycythemia vera; ET, essential thrombocythemia; and CIMF, chronic idiopathic myelofibrosis.

LeukemiaNet; Andreas Reiter, personal written communication 9 August 2004). Simultaneously, further observations on the clinical features of these patients, perhaps by the development of multinational registries, may help predict those patients most likely to be fusion gene positive and to benefit from imatinib. ■

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CLINICAL OBSERVATIONS

Comment on Palumbo et al, page 3052

Too old for transplantation: think again

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The role of high-dose therapy in the management of multiple myeloma in patients older than 65 years has, to date, been uncertain. The current article establishes both survival benefit and improved response duration in patients up to the age of 70 years with multiple myeloma.

There are 2 studies that have demonstrated the survival advantage of high-dose therapy compared with conventional chemotherapy. In the first of these studies, sponsored by the Intergroupe Francophone du Myélome (IFM),[1] patients' median age was 57 years and all were younger than 65 years. In the Medical Research Council (MRC)[2] study, the median age was 55 years, and the oldest patient entered was 66 years. These studies do not help make an evidence-based decision on the value of high-dose therapy in patients older than 65 years. In fact, the Myélome-Autogreffe Group (MAG)[3] reported patients aged 55 to 65 years where high-dose therapy produced no improvement in event-free or overall survival compared with conventional therapy.

A number of retrospective reports on the outcomes following stem cell transplantations in older patients are given in Table 1. The treatment-related mortality in patients older than 65 years is 8% and event-free and overall survival appear shorter in older patients. Most centers, due to high treatment-related mortality, have reduced the conditioning dose of melphalan in older patients to 140 mg/m^2. Palumbo (see "Torino" in the table) reported a case-control series of patients receiving 100 mg/m^2 melphalan with a contemporaneous group of patients receiving standard therapy and demonstrated a superior event-free and overall survival for the high-dose therapy group. A report from the ABMTR analyzing patients younger than and older than age 60 years showed no difference in outcome. These studies, which establish the safety and feasibility of stem cell transplantation in the elderly, however, do not demonstrate the superiority of high-dose therapy.

Study	No. of patients	Age, y	EFS, mo	OS, mo
MAG[3]	190	55-65	NS	NS
Little Rock[4]	49	> 65	18	40
Little Rock[5]	70	> 70	15	24
Torino[6]	53	> 60	34	56+
ABMTR	110	> 60	NS	NS

Transplantation in older patients. EFS indicates event-free survival; OS, overall survival; ABMTR, American Bone Marrow Transplant Registry; and NS, not significant compared with younger patients.

An attempt to improve the results with conventional dose therapy was reported in IFM trial 9501. There were 489 patients aged 65 to 75 years randomized to melphalan and dexamethasone; dexamethasone; dexamethasone and interferon; and standard melphalan and prednisone. Dexamethasone-based regimens did not improve overall survival for patients older than 65 years.

In the current issue of *Blood,* Palumbo and colleagues report patients aged 50 to 70 years who were randomized to standard melphalan/prednisone versus tandem cycles of high-dose melphalan at 100 mg/m^2; 46% were older than 65 years. Strictly defined near-complete responses were seen in 25% of patients aged 65 to 70 years. The event-free and overall survival rates for the high-dose group were superior. Patients aged 65 to 70 years had a median survival of 58 months compared with 37 months for patients on standard therapy. This randomized study supports using high-dose therapy for patients older than 65 years.

For patients older than 65 years in the United States, Medicare does not reimburse for tandem cycles of therapy, so it would be difficult to follow this exact protocol. Perhaps a single cycle of therapy at 140 mg/m^2 will produce benefits not achievable with standard therapy.

What should the next studies be? Transplant studies demonstrate benefit compared with conventional therapy, however, the nature of conventional therapy is changing. The introduction of thalidomide and bortezomib are altering our concepts of initial therapy for patients. There were 56 newly diagnosed myeloma patients given melphalan and prednisone with the addition of thalidomide at 100 mg per day. A complete response was seen in 22% of patients, with an overall response rate