inside blood

AIDS lymphomas: beginning of an EPOCH?

Highly aggressive lymphomas emerge in the setting of acquired immunodeficiency syndrome (AIDS) due to human immunodeficiency virus 1 (HIV-1) infection. Prior to effective treatment for HIV, AIDS-related lymphomas (ARLs) were extremely difficult to effectively treat because of poor tolerance of chemotherapy and concurrent superinfections. That preantiretroviral therapy era was marked by efforts to define minimally toxic lymphoma therapy, recognizing that the balance between fatal diseases was often on a razor's edge. These dark days remain for most of the world's infected, but for those with access to highly active antiretroviral therapy (HAART), there has been a dramatic change. ARL is now a highly curable disease. What then is the best therapy? Is this the same disease as that seen prior to the advent of HAART? And how might cancer chemotherapy be combined with the panoply of anti-HIV drugs?

Little and colleagues (page 4653) have gone a long way to addressing all 3 questions. They provide highly encouraging results using a dose-adjusted infusional regimen, EPOCH. The 74% CR (87% overall) and 73% progression-free survival at 53 months appears to be a substantial improvement over what has been seen with more standard CHOP chemotherapy or other infusional regimens. The results need confirmation in a multicenter trial, and such is already underway through the US AIDS Malignancy Consortium. Why might an infusional approach be particularly active in this tumor? Infusional regimens are thought to be more effective against highly proliferative tumors, a feature the authors document in 85% of ARLs. Might responses be more likely in the setting of HAART because of differences in tumor biology? This likelihood, too, is supported by their study. Unlike ARLs seen before the era of HAART, these tumors have 2 features associated with an improved outcome: they have low BCL-2 expression and they likely represent a germinal center, rather than a postgerminal center, B cell. Finally, how can the complicated anti-HIV medications be given in the context of cancer chemotherapy? Prior studies continued both therapies, restricted anti-HIV medications, and measured drug levels and toxicities, with favorable results. The ever-shifting sand of antiretroviral drugs simply does not allow such an approach any longer. Rather, Little and colleagues stopped all anti-HIV drugs and noted transient, but tolerable, increases in HIV cells and decreases in CD4 cells. Both parameters returned to baseline or better within 6 to 12 months following the resumption of HAART. Therefore, Little and colleagues have provided new information on an ARL therapy to pursue, evidence for evolving tumor biology based on use of HAART, and a practical strategy for handling the complex balance of anticancer and anti-HIV therapy.

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Major link between mast cells and the idiopathic hypereosinophilic syndrome

The idiopathic hypereosinophilic syndrome (IHES) is characterized by sustained severe peripheral blood eosinophilia (more than 1500 eosinophils/mm^3) and the presence of eosinophil-associated end-organ damage in a patient with no identifiable causes for the eosinophilia (eg, malignancy or infection). Despite the fact that IHES is a rare problem, the disease has received a significant amount of research attention, especially of late. Notably, the molecular basis for IHES (in a subset of patients) has recently been shown to involve an interstitial deletion in chromosome 4, which results in the generation of a fusion protein between the platelet-derived growth factor receptor α *(PDGFRA)* gene and a previously uncharacterized gene, *FIP1L1* (Cools et al, N Engl J Med. 2003;348:1201-1214). Notably, the fusion protein is susceptible to imatinib (Gleevec) treatment; interestingly, this drug has recently been shown to be effective in a subset of patients with IHES. These results suggest that many cases of IHES are actually myeloproliferative clonal disorders. As such, these results challenge the conventional classification of hypereosinophilic syndromes that has historically distinguished IHES from eosinophilic leukemia.

In this issue Klion and colleagues (page 4660) extend these important observations in a landmark study that provides further evidence that this subset of patients has a myeloproliferative disease variant. In particular, the authors examine levels of serum tryptase, a mast cell–derived product that has been previously associated with myeloproliferative disorders and systemic mastocytosis. Notably, the investigators found that 9 of 15 patients with classic IHES had elevated levels of serum tryptase. Importantly, this tryptase-positive subset of patients had a markedly worse disease course, including extensive end-organ damage and a higher mortality rate. Of even greater interest, all tryptase-positive patients harbored the *FIP1L1-PDGRFA* gene fusion and all responded to imatinib therapy. Whereas the tryptase-positive IHES patients met minor criteria for systemic mastocytosis, the authors presented evidence that distinguished these patients from classic systemic mastocytosis (eg, lack of bone-marrow mast-cell clusters or abnormal mast-cell phenotypes). Indeed, mast-cell products (eg, TNF-α, IL-5, proteases, and eotaxin) activate eosinophils; conversely, eosinophil products (eg, major basic protein) activate mast cells. Although both cell types are involved in allergic diseases, previous studies have distinguished their lineage commitment. For example, mast cells are primarily c-Kit-ligand–dependent whereas eosinophils are primarily IL-5–dependent. These results implicate direct action between mast cells