is a more systemic disease with a diverse and complex phenotype. In particular, they believe that cardiovascular amyloidosis appears to be underdiagnosed. In the affected persons, the authors found a high incidence of cardiovascular atheromatous disease predating the evolution of proteinuria or renal impairment by many years; there was also a strong family history of coronary/vascular disease in these patients. The authors document deposition of a fibrinogen variant in vascular walls and in atheromatous plaques, thus linking variant fibrinogen amyloidosis and atherosclerosis. They conclude that the cardiovascular findings are unlikely to be due solely to renal failure, in contrast to Gillmore et al.[4] Stangou et al suggest that direct amyloid deposition in vascular walls may be the first step in a disease process that leads to impaired endothelial function, and that nephrotic syndrome with hyperlipidemia and hypertension may then facilitate atheroma formation (see figure). If this is indeed confirmed by further studies, this hypothesis will associate yet another type of amyloidosis (ie, in addition to AA, AApo-AI, and AApo-AII) with atherosclerosis. These findings may be relevant to the care of AFib carriers and nonscreened family members.

The second major focus of the paper is reporting the results of hepatorenal transplantation in a subset of these patients. This approach is predicated on the authors' belief that Afib is a systemic and serious disorder, affecting more organs than solely the kidneys, and that therefore renal transplantation can be compromised by ongoing damage to other tissues and to the new renal graft. In their series of hepatorenal transplant recipients, the authors report a halt in the progression of amyloid deposition, and some evidence for improvement in pretransplantation symptoms, including gut dysmotility. Because hepatorenal transplantation appears to prevent disease progression and allow reversal of some organ dysfunction, the authors advocate early or even preemptive transplantation of liver alone, that is, before renal failure and significant cardiovascular amyloidosis develop, especially because the latter may preclude transplantation. This is certain to be a contentious issue, but Stangou et al provide important data to consider in designing the best approach for individual patients.

Phenotype variability is well known in transthyretin amyloidosis and largely depends on the type of mutation. With 6 amyloidogenic mutations in the fibrinogen A α-chain reported to date, and the discovery of considerable phenotypic variability, the possibility of a similar phenotype/genotype relationship in AFib also appears probable. The cohort size in studies to date precludes detailed phenotype/genotype conclusions, but it is likely that in the future, specific mutations may be linked to variations in disease penetrance and progression.

While the clinical spectrum of the amyloidoses and their available therapies are evolving, the important message to the readership of *Blood* is that diagnosis of amyloidosis must be sought early in the disease process and its type determined correctly. It should never simply be "assumed" to be AL.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● CLINICAL TRIALS

Comment on Dunleavy et al, page 3017, and Sparano et al, page 3008

HIV-associated lymphoma

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The role of infusional chemotherapy and the value of rituximab with chemotherapy have not been clearly defined in patients with HIV-associated lymphoma. Recent data have provided insights into these questions.

Although the optimal therapeutic strategies for patients with HIV-associated lymphoma have remained controversial, recent studies by Dunleavy et al and Sparano et al in this issue of *Blood* have brought clarity to several contentious issues.[1,2] First, should rituximab be included within the regimen? Second, does the benefit of a prolonged infusion, such as the EPOCH regimen,[3] outweigh the inconvenience and cost? Third, should antiretroviral therapy be suspended during chemotherapy? Fourth, are there subtypes of lymphomatous disease that should be treated differently than others? Fifth, is FDG-PET scanning a useful restaging and prognostic tool in HIV lymphoma?

The addition of rituximab to the CHOP regimen has resulted in remarkable prolongation in long-term disease-free survival among patients with HIV-negative diffuse large B-cell lymphoma (DLBCL),[4] and early results among patients with HIV-associated lymphoma appeared also to show benefit.[5] Unexpectedly, a randomized phase 3 study of CHOP with or without rituximab, performed by the AIDS Malignancy Consortium (AMC), found only a trend toward greater efficacy in patients on the rituximab arm, with a statistically significant increase in death due to infection.[6] When analyzed more carefully, these infectious deaths occurred primarily among patients with severe immunodeficiency. If patients with CD4 lymphocyte counts less than 50/μL were excluded from the analysis, no significant difference in infectious death was seen. Severe HIV-related immunodeficiency in itself has been associated with an increased risk of septic death, even in the absence of chemotherapy.[7] Nonetheless, rituximab has been associated with various viral infections, as well as progressive multifocal leukoencephalopathy and hepatitis B reactivation, and could theoretically be a concern.[8] The results of the AMC study served to emphasize these concerns, and was in all likelihood responsible for a change in treatment paradigm away from the use of rituximab in HIV-infected patients. In this issue of *Blood*, a subsequent randomized phase 2 study from the AMC did *not* show an increased risk of

infectious death among patients receiving concomitant chemotherapy and rituximab.[2] The study by Dunleavy et al, also reported in this issue, has again confirmed the efficacy of rituximab, allowing an abbreviated course of infusional EPOCH while noting no treatment-related deaths or new opportunistic infections. Whereas it behooves the clinician to be aware of the potential for rituximab-related infections, especially in patients with severe immunocompromise, it is time to put this question to rest. Similar to the case in HIV-negative lymphoma, patients with HIV-associated DLBCL clearly benefit from the use of concomitant rituximab and chemotherapy.

Results of infusional short-course EPOCH with double-dose rituximab (SC-EPOCH-RR), even when given for only 3 or 4 cycles, were remarkably good in the Dunleavy study, with 85% progression-free and 68% overall survival at a median follow-up of 5 years. CHOP-based regimens have not been associated with these kinds of results, and the AMC studies of EPOCH[2] and of CHOP[6] would seem to confirm that infusional EPOCH is the superior regimen in the setting of HIV-associated DLBCL. Greater ease of administration would be nice, but a shortened total treatment time may partially compensate for the inconvenience of a prolonged infusion. In the final analysis, the patient deserves to receive the regimen associated with the best chance of long-term survival.

Tumor histogenesis was found to be the only factor associated with lymphoma-specific outcome in the Dunleavy study,[1] with non–germinal center (GCB)–DLBCL patients faring significantly worse than their GCB-DLBCL counterparts. Although optimal techniques to allow confirmation that these non–GCB-DLBCL cases did, in fact, represent the activated B-cell type of DCLBC, still, this conclusion is quite likely and indicates that new treatment paradigms will be necessary in these persons, be they HIV-infected or not.

Although multiple aspects of the pathogenesis and optimal therapy of DLBCL appear similar among HIV-negative and -positive patients, the Dunleavy study has shown that the utility of FDG-PET scanning in the 2 populations is quite different.[1] Whereas FDG-PET after 2 cycles of SC-EPOCH-RR had an excellent negative predictive value, a positive scan was not necessarily clinically meaningful. This would be consistent with the fact that FDG-PET may be positive in the setting of inflammation or infection, conditions that are not uncommon among HIV-infected patients. With the Dunleavy data in mind, the role of FDG-PET in patients with HIV-associated lymphoma will clearly require additional evaluation prior to clinical adoption.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● IMMUNOBIOLOGY

Comment on Baessler et al, page 3058

CD137 in NK cells

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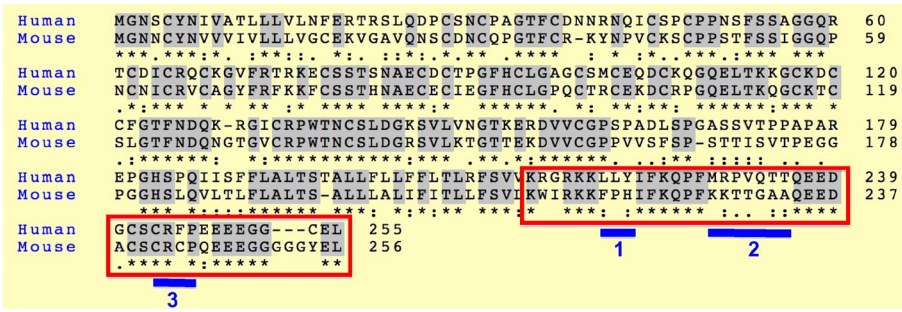
In this issue of *Blood*, Baessler and colleagues find that the engagement of CD137 on mouse and human NK cells had opposite effects in that CD137 functioned as an inhibitory receptor in human NK cells and as a stimulatory receptor in mice.[1] As NK cells emerge as potential therapeutic targets for leukemia treatment, the authors also investigate the expression of CD137L by leukemic cells. A significant level of expression was found for monocytic AML, which could contribute to immune evasion.

CD137, also known as 4-1BB, is a member of the TNFR super family. CD137 is closely related to CD27, OX40, and CD30. It is up-regulated on mouse and human T cells upon activation.[2] It has long been recognized as a costimulatory molecule for T cells. CD137 engagement by CD137L on antigen-activated T cells increases proliferation, effector functions, and survival, in both mouse and human. Other members of the TNFR family such as OX40 or CD27 act similarly, and it is currently unknown whether these different receptorsact synergistically, sequentially, or via a more complex crosstalk.[2,3] The use of anti-



Alignment of human and mouse CD137 protein sequences. The red box corresponds to the intracellular regions. Blue bars highlight divergences between mouse and human. Stars indicate identity, and dots conservation in the type of amino acids between sequences.