65% and more than 50% of them had adverse cytogenetics. Finally, 55% of patients had secondary AML. Overall, of the 84 patients receiving T+E, 21 (25%) achieved CR, with a median CR duration of 9.8 months. Patients achieving CR had a median age of 77 years and their median survival was 22 months, with 14 (67%) surviving more than 1 year and 9 (43%) still living at 15.5+ to 36+ months. These data compare favorably with results achievable after conventional chemotherapy as well as with those reported by using single agent T or T + low-dose ARA-C. Previous study of single agent T had considered a 21-day schedule, which was not feasible in combination with E. In contrast, the same etoposide schedule was better tolerated when tipifarnib was administered for 14 days, with acceptable occurrence and severity of mucositis, a well-known effect of etoposide, and neurotoxicity.

In the conclusion, the above data, along with recently published results achieved with other new drugs such as clofarabine and cloretazine, demonstrate encouraging therapeutic results in a previously very difficult to treat patient population of poor-risk older AML patients. It is now time to allocate these patients into upfront experimental clinical trials that avoid unnecessary toxicity, not counterbalanced by substantial clinical benefit. The search of preclinical and clinical models, based on the combination of new agents with old drugs as in the study by Karp et al, could represent a successful model for future therapeutic approaches in AML in the elderly and would be extended to high-risk relapsed patients, independent of age.

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Comment on Greinacher et al, page 4970, and Warkentin et al, page 4963

Nothing typical about HIT

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In this issue of Blood, 2 articles describe the evolution of the PF4/heparin immune response and provide further proof that the HIT immune response is anything but typical.

The immune response to PF4/heparin, which is the serologic basis of heparin-induced thrombocytopenia (HIT), is unlike any other known drug-induced hypersensitivity reaction. Whereas most reactions to drugs are rare, idiosyncratic, and long-lived, the immune response triggered by heparin is fairly common, predictable in certain clinical settings, and short-lived in most cases. The immunologic basis of these atypical features in HIT is unknown.

Animal models of PF4/heparin antibody formation have recently been developed to gain insights into the immune pathogenesis of HIT. Modeling the disease in animals, however, has been hampered by a lack of knowledge of the early events related to human PF4/heparin seroconversions. In this issue of Blood, Greinacher and colleagues and Warkentin and colleagues address some of the critical gaps in our understanding of the HIT immune response. Although both studies employ the same general approach to studying the timeline of seroconversions, the goals of each study differ. The study by Greinacher and colleagues provides a detailed serologic analysis of the PF4/heparin immune response; the study by Warkentin et al focuses on characteristics of seroconversions leading to clinical complications in HIT.

Greinacher et al document the course of PF4/heparin seroconversions in a cohort of 435 patients treated with thromboprophylactic doses of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Using serially collected samples from these patients, the authors characterize the temporal course of PF4/heparin antibody formation, isotype patterns, and the trajectory of the immune response during continued heparin therapy. They note that more than 90% of the seroconversions occur within 4 to 14 days of heparin therapy while 6.6% occur before day 4 and another 1.6% occur after day 14. Although patients with a “strong” immune response (defined as a change in optical density [OD] or ΔOD of > 1.0 from baseline signal) showed a trend toward earlier onset of PF4/heparin antibodies as compared with patients with “weaker” immune response (ΔOD < 1.0), this did not reach significance. In the subset of patients analyzed for isotype patterns (n = 58), the authors were unable to document any differences in the timing of onset of the individual immunoglobulins (IgG, IgA, or IgM). The authors provide 2 additional intriguing observations on the trajectory of the HIT immune response during heparin therapy. They note that antibody responses “peak” by day 9 to 10 of UFH/LMWH therapy and decline thereafter, despite continuation of therapy. They also note that in a LMWH extension trial in which investigators were blinded to findings of PF4/heparin serology, 31 seropositive patients (half of whom had platelet activating antibodies) received an additional 3 months of LMWH thromboprophylaxis without developing clinical HIT.

In the companion paper by Warkentin and colleagues, daily samples from 48 patients (12 patients who develop HIT and 36 patients who manifest only PF4/heparin antibodies) are analyzed over time to document serologic features associated with HIT. The authors note that although patients with and without HIT have similar time to onset of the immune response (median interval of 4-5 days), the time to onset of IgG isotype (interval onset time of 4.7 days in HIT patients and 6 days in non-HIT patients) and magnitude of the IgG response (median OD, HIT = 1.63 vs non-HIT = 0.94) differs in the 2 groups. Importantly, the authors provide a “timeline” for development of clinical complications relative to seroconversions. They show that
A new role for Pk: finding the 1 in a million

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Blood group antigens can have critical functions beyond the red blood cell. In this issue of Blood, Lund and colleagues demonstrate a role for Pk in HIV entry, providing biologic insight, identifying potential therapeutic target motifs and expanding the intersections of hematology, transfusion medicine, and infectious disease.

It is said that there are more than 400 blood group antigens on the red blood cell and of these, about 40 have known clinical significance. Significance in this context refers to transfusion-related concerns, typically meaning the ability of an antibody, when in proximity to the cognate antigen, to cause hemolysis—intravascularly, extravascularly or in utero (as in transfusion reactions or hemolytic disease of the newborn). More recently using precise molecular methods, investigators have been able to ascertain and assign biologic functionality and thus clinical significance to a number of blood group antigens, now including Pk.

Ppk or Gb3 is a member of the GLOB collection which includes P, Pk, and LKE. Ppk is related to the P blood group system discovered by Landsteiner and Levine in 1927 and has its name “as it was the first letter following M, N and O, which had already been used.”1,2 Biochemically, Ppk is Galα(1→4)Galβ(1→4)Glc- CER (synthesized from lactosylceramide [or GalB(1→4)Glc- CER] by the sequential addition of galactose via α(1→4) galactosyltransferase encoded in the Ppk gene), which when acted upon by the enzyme encoded by the presence of the P gene becomes P.1 Alternatively, lactosylceramide can be modified to Pk via less understood reactions. In addition to the presence of Ppk on erythrocytes, this antigen is also found on epithelial cells, monocytes, and B cells where it takes on the designation of CD77. Importantly, while Pk is found in approximately 80% of whites, Ppk is found in only about 1 in a million.

Previously, this group has shown: (1) an accumulation of Ppk, in patients with Fabry disease due to reduced α-galactosidase conferred resistance to R5 HIV-1,1,3 and (2) a soluble analog of Ppk inhibits HIV infection in vitro.4 The current report also builds on the report of Fantini et al., demonstrating that HIV-infected mononuclear cells have increased Pk expression.5

It is upon this background that Lund et al assessed the susceptibility to HIV–1 of peripheral blood mononuclear cells (PBMCs) from blood donors high in Pk (the Ppk phenotype) compared with those with essentially no Pk expression (the...
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