Tipsifarnib and etoposide for older AML patients: from bench to bedside

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In this issue of Blood, Karp and colleagues describe preclinical and clinical effects of the combination of tipsifarnib with etoposide. The study represents an admirable example of successful translation of in vitro data to a phase 1 clinical trial.

Comment on Karp et al, page 4841

Novel therapeutic approaches are needed for older patients with acute myeloid leukemia (AML), namely for those who are not likely to benefit from conventional chemotherapy because of either poor performance status or adverse biologic characteristics at diagnosis.1 Tipsifarnib (T) is a specific and potent farnesyltransferase inhibitor that demonstrates in vivo and in vitro activity against different human malignancies. However, the activity of tipsifarnib in a variety of intracellular pathways that have been specifically implicated in the leukemogenesis makes it an especially attractive agent for use in AML.2 Apart from the appealing biologic background, the oral administration and favorable toxicity profile of the drug has particularly stimulated clinical research on tipsifarnib in older patients with AML, as single agent or in combination. However, a large multicenter trial that compared tipsifarnib to best supportive care failed to demonstrate any advantage in terms of survival.3 In addition, the use of the drug in association with low dose ARA-C resulted in excess death, and that study was prematurely closed.4 The role of tipsifarnib as maintenance therapy, as well as the possibility of combination therapy with standard induction chemotherapy is currently under investigation in AML.5,6

In the study by Karp et al, preclinical data clearly demonstrated that tipsifarnib inhibits signaling downstream of mTOR and enhances the antiproliferative effects of etoposide (E) in AML cell lines and clinical specimens, suggesting a role for Rheb, a small G protein that deserves further investigation, as far as its role into leukemogenesis is concerned.7 In addition, the authors showed that treatment with T+E in vivo is accompanied by drug-induced increases in histone H2AX phosphorylation and, to a lesser extent, DNA fragmentation in AML marrow blasts. This was coupled with the suggestion that achievement of complete remission (CR) may be associated with modest but measurable increases in both parameters. While the precise mechanisms leading to synergism of the combination remains to be clarified, these findings represent the biologic background of a multicenter clinical trial aiming at demonstration of the safety and potential efficacy of T+E in elderly AML patients, who are not candidates for conventional induction treatment on the basis of both host clinical features and unfavorable disease biology. It is noteworthy that the proportion of patients 75 years or older in this study was...
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 particularly 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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**REFERENCES**


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**THROMBOSIS & HEMOSTASIS**

**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...
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