Receptors. Transient expression of WT1 has been detected in small fractions of uncommitted and lineage-committed hematopoietic progenitor cells, but the functional role of WT1 in the development and regulation of the normal hematopoiesis is currently not well characterized. Further, constitutive expression of wild-type or mutant WT1 has been demonstrated in a variety of hematologic malignancies and, particularly, in blasts of nearly all acute leukemias irrespective of lineage-specificity. Therefore, WT1 expression may be regarded as a nonspecific “panleukemic” molecular marker, and quantitative monitoring of WT1 transcripts holds promise to become a universal tool for the evaluation of MRD after chemotherapy or HSCT, especially for the approximately 50% of acute leukemias without an established disease-specific gene rearrangement.

This expectation is further promoted by the work of Ogawa and coworkers (page 1698), which strongly supports that sequential analyses of WT1 transcript expression levels in marrow cells after allogeneic HSCT can be used to reliably predict leukemic relapse and responses to immunomodulatory interventions against imminent or overt posttransplantation relapse. If confirmed by larger prospective studies, this work would substantially contribute to close the diagnostic gap of MRD detection and to define universal MRD thresholds for clinical decision-making after HSCT.

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Expanding uses of high-dose factor VIIa

Recombinant FVIIa is approved in many countries as a “bypassing” agent that promotes hemostasis in patients with congenital or acquired hemophilia with inhibitors (Hedner, Adv Exp Med Biol. 2001;489:75-88). In addition, FVIIa has now been used off label in a range of conditions including thrombocytopenia, platelet function defects, liver transplantation, and after trauma or surgery. While few controlled clinical trials have been done, FVIIa appears to be remarkably safe and effective in a variety of settings.

The mechanism of action of FVIIa has been best studied in models of hemophilia. Hemophilia is a failure of platelet surface FXa generation. Our studies and those of others suggest that FVIIa acts independently of its usual cofactor, tissue factor, to enhance platelet-surface thrombin generation (Hoffman et al, Semin Hematol. 2001;38:6-9). FVIIa does this by partially restoring platelet-surface FX activation that is lacking in the absence of the FIXa/FVIIIa complex. Others have suggested that FVIIa also speeds platelet activation. A platelet-dependent mechanism explains why FVIIa does not cause systemic activation of coagulation, since the activated platelets on which FVIIa acts localize it to sites of injury.

FVIIa is one of the few treatment options for patients with Glanzmann thrombasthenia. While the effects of FVIIa in ex vivo models of thrombocytopenia have been studied to a limited extent, the mechanism by which it improves hemostatic function in Glanzmann patients may or may not be similar (Monroe et al, Semin Thromb Hemost. 2000;26:373-377). The paper by Lisman et al in this issue (page 1864) provides the first experimental work on a mechanism of action for FVIIa in platelet function defects. This work shows that FVIIa can enhance platelet adhesion in a flow chamber model. This effect depends on thrombin generation but is independent of tissue factor. The authors provide an experimental rationale for the effectiveness of high-dose FVIIa in patients with platelet function disorders and suggest that the mechanism of action may be similar to that in hemophilia.

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Is the cure worse than the disease?

No, it isn’t. The worrisome observations of the delayed development of t-MDS/AML in some lymphoma patients after HDC and AHSC can not obscure the overall success of this procedure in selected patients. That said, t-MDS/AML is the serious nonrelapse problem in these patients, and efforts to identify risk factors that would reliably identify patients at high risk of developing t-MDS/AML would be beneficial, both in focusing increased study of such patients and potentially, to develop therapies to decrease the impact of this (currently) very lethal complication.

The report of Metayer and colleagues in this issue (page 2015) adds to a growing, if inconsistent, literature regarding risk factors. Using detailed data from 12 institutions in the Autologous Blood and Marrow Transplant Registry, they performed a case-control study using 56 patients who developed t-MDS/AML and 168 matched control patients from a larger group of 2739 lymphoma patients receiving transplants at these centers over 6 years. The cumulative incidence of t-MDS/AML was 3.7% at 7 years. (For unclear reasons, this is lower than reported in other published series, and it would be unrealistic to state that the “true incidence” is known with certainty.) In multivariate analysis, exposure to certain alkylating agents with a known leukemogen pedigree (especially nitrogen mustard and chlorambucil, with a statistical significance dose effect), as well as conditioning regimens that included TBI, but only at doses of 1320 cGy, were associated with a statistically significant increased risk of developing t-MDS/AML. The use of reconstituting cells from either steady-state or mobilized blood was associated with an increased risk as well, albeit a nonsignificant one. Thus, both pretransplantation and transplantation-related factors were implicated.

The authors are to be commended for this effort, which clearly gives additional direction to strategies or techniques that might decrease this risk. That said, significant limitations of this study must be acknowledged; to a large degree, these limitations are generic to studies evaluating “late events” that require prolonged follow-up for delineation in a field in which evolutionary therapy changes are routine. For example, this analysis includes both Hodgkin and the
non-Hodgkin lymphomas, whereas other series focused on one or the other, in the main. This obviously may have implications on the specific therapy given and the contribution to the MDS/AML. Also, the routine use of the nitrogen mustard, chlorambucil, and perhaps other suspect drugs has been greatly curtailed in the past decade, as the CHOP and ABVD regimens have become standards of care for many non-Hodgkin and Hodgkin lymphoma patients, respectively. In the same context, the use of local radiotherapy (a potential contributor exonerated in this analysis) as either primary therapy or as an adjunct to the above or similar regimens appears to be declining. Also, the use of TBI is not considered critical and may also be declining in use. Thus, the warning about these specific agents arrives as the danger is receding.

In contrast, the issue of potential increased risk from the use of reconstituting cells obtained from the blood is more complex; this technique has almost fully supplanted marrow harvest in autotransplantation and has been the standard of care for nearly a decade. Since the main advantages of using mobilized blood reconstituting cells are usually not reflected onto major outcome parameters, further delineation of this point is critical to ensure we are not increasing t-MDS/AML by the use of this technique.

What lessons can be learned from this experience? First, a prolonged period of observation of patients is necessary to delineate late complications such as t-MDS/AML. Next, before we breathe a sigh of relief at the passing of the routine use of agents such as the nitrogen mustard and chlorambucil, we may get another chance to revisit this situation as long-term effects of increased use of topoisomerase-II inhibitors and possibly radioimmunotherapies are assessed. In addition, we will need to become more facile at being able to identify high-risk patients on an individual rather than a population basis; conventional cytogenetics are clearly inadequate, but other techniques (perhaps including FISH, SKY, or selective gene array studies) may be more suitable.

Finally, however, we should again take note of the potency of the HDC/AHSCT technique in lymphoma patients: thousands of such patients are alive today because of this procedure; moreover, refinements of HDC/AHSCT—as well as other strategies (eg, the use of reduced-intensity allografts)—may be expected to further improve results. Nonetheless, we must be vigilant to the development of t-MDS/AML using our newer techniques and develop methods to identify, prevent, and/or treat such patients early in their course.

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