studying the role of cullin-mediated ubiquitination in vivo. The investigations of Waning et al have already revealed essential pathways in hematopoietic and other regenerating tissues; there are likely more to be discovered.

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Comment on Marks et al, page 426

Allografting in ALL: the net widens

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The introduction of the GVL effect is the single most efficacious therapeutic intervention in the management of patients with ALL who are in complete remission.

Three decades have passed since the first report in humans of the graft-versus-leukemia (GVL) effect, which was most significant in patients with acute lymphoblastic leukemia (ALL).\(^1\) The relapse rate was 2.5 times lower in allogeneic marrow recipients with graft-versus-host disease (GVHD) than in patients without GVHD. Despite this early report, the incorporation of allogeneic transplantation into clinical practice in ALL has been slow, especially for patients in first remission. Initially, it was employed only for ALL patients with the Philadelphia chromosome\(^2\) and was followed by several reports on the use of allogeneic transplantation for high-risk ALL patients in first remission.\(^3\) Recently, a very large prospective trial, the international Medical Research Council/Eastern Cooperative Oncology Group (MRC/ECOG) study, reported on the benefit of allografting for adult patients with ALL in first complete remission, with the greatest effect seen in patients with standard risk. In older patients, high-treatment-related mortality (TRM) abrogated the beneficial antileukemic effect due to GVL.\(^4\)

All of these investigations used HLA-matched siblings. The increasing use of matched unrelated donors in ALL\(^5\) has given further hope to the majority of patients who do not have a sibling donor.

Marks and colleagues in this issue of Blood have addressed this matter by reporting on an observational study conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR) on 169 unrelated donor transplants in adults with Philadelphia chromosome-negative ALL in first complete remission. More than 90% of patients were at high risk. Approximately half of the patients had acute GVHD and more than 40% of patients had chronic GVHD. The TRM was about 40%. Despite this, about 40% of patients appeared to be long-term survivors, which is significantly better than what one would expect from high-risk ALL patients who would be treated without transplantation. As the authors themselves note, caution must always be exercised when interpreting retrospective data from registries, and historical comparisons have similar pitfalls. Nevertheless, this is an important study; the data provided by it confirm the feasibility and importance of the antileukemic effect of allogeneic transplants when using matched unrelated donors. Clearly, this approach is encouraging and needs to be pursued in prospective studies.

At least 2 major issues remain. First, why confine this approach to patients at high risk? Given that the best data on the use of allogeneic transplantation in first complete remission in ALL have been for patients at standard risk,\(^4\) the potential for increasing the donor pool to include matched unrelated donors should be studied in this more favorable risk category. Second, the lack of a significant survival benefit for older patients is a high risk in the international ALL trial was due to the high TRM in older adults, much like in the report from the CIBMTR. While there are increasing data on the use of reduced-intensity allogeneic transplantation in AML, the data on the use of such conditioning regimens in ALL are scanty. As the majority of adult patients with ALL are older than 40 years of age, this modality, both for related and unrelated donor transplants, is an attractive concept that must be prospectively evaluated, especially in light of the fact that the incidence of unfavorable cytogenetics, such as the Philadelphia chromosome, increases with age and approaches 50% in patients with B-lineage ALL who are older than 50 years of age.

While the pendulum is swinging to more fully embrace the GVL effect in ALL in first remission, this must be done cautiously and in carefully controlled prospective clinical trials.

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