observed in cells undergoing crisis in vitro: this phase of cell life is known to be associated with an extremely high level of genomic instability. Furthermore, the authors report that the presence of critically shortened telomeres was associated with severe genomic instability as shown by the presence of complete telomeric loss events, fusion events, and genomic rearrangements concentrated in telomeric regions. The presence of dysfunctional telomeres was more common but not exclusively found in patients with poor prognostic features (Binet stage C, VH-unmutated status, and high Zap-70 expression), suggesting that a proportion of patients might show evidence of telomeric dysfunction even at early disease stages. Taken together, these results provide convincing evidence that crisis-like phenomena associated with dysfunctional telomeres play a role in CLL progression (see figure) and might be involved in critical events such as chromosome 17p loss. Finally, as severe telomere attrition is not found exclusively in CLL but rather occurs in many hematologic and solid tumors, a reasonable hypothesis can be made that tumor progression associated with critical telomere shortening might also be of relevance in other tumors.

The report has a few limitations, in particular the small number of patients studied and lack of strong clinical correlations. An association with poor prognostic features was observed but the impact of TL determination by STELA on survival, treatment requirement, drug sensitivity, and so on still needs to be addressed in large cohorts of CLL patients with adequate follow-up. As TL proved of high prognostic value even when measured with less sophisticated tools, I expect to find these correlations highly positive with STELA also. From a more speculative point of view, the ability of CLL cells to actually bypass the senescence checkpoint and enter crisis in the absence of permitting lesions such as, for example, p53 loss or chromosome 11 deletion—both quite uncommon events in early CLL—is not fully understood. Clearly, the impact of a telomere-related progression mechanism would be broader if proven to occur even in the absence of these major genetic defects.

Despite these limitations, this report establishes a clear link between telomere deregulation, genomic instability, and CLL progression. Future studies are required to address the relative impact of different stressors on telomere dynamics (including proliferation drive, specific genetic lesions, microenvironment, host genetic background, treatment, and so on) that might explain the large variability of TL in CLL patients. From a more general point of view, it will be fascinating to see if the same mechanisms come into play in other human cancers.

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

REFERENCES

1. Lin TT, Letsolo BT, Jones RE, et al. Telomere dysfunction and fusion during the progression of chronic lymphocytic leukemia: evidence for a telomere crisis. *Blood*. 2010;116(11):1899-1907.
2. Kim SH, Kaminker P, Campisi J. Telomeres, aging and cancer: in search of a happy ending. *Oncogene*. 2002;21(4):503-511.
3. Bisoffi M, Heaphy CM, Griffith JK. Telomeres: prognostic markers for solid tumors. *Int J Cancer*. 2006;119(10):2255-2260.
4. Damle RN, Batliwalla FM, Ghiotto F, et al. Telomere length and telomerase activity delineate distinctive replicative features of the B-CLL subgroups defined by immunoglobulin V gene mutations. *Blood*. 2004;103(2):375-382.
5. Grabowski P, Hultdin M, Karlsson K, et al. Telomere length as a prognostic parameter in chronic lymphocytic leukemia with special reference to VH gene mutation status. *Blood*. 2005;105(12):4807-4812.
6. Rossi D, Lobetti Bodoni C, Genuardi E, et al. Telomere length is an independent predictor of survival, treatment requirement and Richter's syndrome transformation in chronic lymphocytic leukemia. *Leukemia*. 2009;23(6):1062-1072.
7. Poncet D, Belleville A, t'kint de Roodenbeke C, et al. Changes in the expression of telomere maintenance genes suggest global telomere dysfunction in B-chronic lymphocytic leukemia. *Blood*. 2008;111(4):2388-2391.
8. Hills M, Lansdorp PM. Short telomeres resulting from heritable mutations in the telomerase reverse transcriptase gene predispose for a variety of malignancies. *Ann N Y Acad Sci*. 2009;1176:178-90. [Erratum. *Ann N Y Acad Sci*. 2009;1179:235.]

● ● ● CLINICAL TRIALS

Comment on Gupta et al, page 1839

Transplantation in AML CR1

Bipin N. Savani VANDERBILT UNIVERSITY

In this issue of *Blood*, Gupta and colleagues report promising results using allo-SCT for patients with unfavorable cytogenetics in AML in CR1.[1] Their data show long-term outcomes for HLA well-matched URD are comparable with those from MSD transplantations. These findings suggest that the allo-SCT approach can be extended to all patients with an HLA-identical donor. The data encourage application of CBT or haploidentical transplantations to these high-risk patients because the outcome of these procedures is improving and expected to be better than chemotherapy alone.

For acute myeloid leukemia (AML) patients with unfavorable cytogenetics, even after achieving complete remission (CR), the probability of disease recurrence without allogeneic stem cell transplantation (allo-SCT) is 80%, and the likelihood of achieving subsequent CR is very low. Gupta et al[1] report improved outcome after allo-SCT in patients with high-risk (HR) AML in CR1 both in the matched sibling donor (MSD) and unrelated donor (URD) settings. As increasing numbers of allo-SCTs are performed from non-MSD stem cell sources, allo-SCT procedures will likely continue to improve (ie, reduced transplantation-related mortality), thereby allowing us to safely extend this curative treatment strategy to patients without MSD.[1,2] Transplants should preferentially be performed on time and not reserved for CR2 in HR patients. Fewer than 20% of HR patients will eventually be able to receive allo-SCT in CR2, as the patient will need to survive the relapse and then be fit enough to undergo allo-SCT in CR2.[3] Although several reports of successful allo-SCT in CR2 with a curative potential of 25% to 30% have been reported, such data are highly selective and should not influence a decision against earlier allo-SCT especially at experienced transplant centers.[3] Moreover, the risk of relapse after URD allo-SCT is higher for patients with unfavorable cytogenetics irrespective of whether the transplant is performed in CR1 or CR2. Because the probability of achieving CR2 after chemotherapy in this group of patients is low, early allo-SCT provides the optimal approach.

The largest and most challenging group of patients with de novo AML falls within the intermediate-risk category. Intermediate-risk patients who achieve CR1 after chemotherapy have a 50% probability of disease recurrence without allo-SCT, and the probability that CR2 can be attained is low. With advances in the molecular classification of AML, such as NPM1, FLT3-ITD, CEBPA, and c-kit, the indications for allo-SCT can now be extended to approximately 40% of patients with AML with no chromosomal abnormalities.[4,5] In a recent meta-analysis by Koreth et al of patients enrolled between 1982 and 2006, a significant overall survival benefit was reported for patients with poor-risk and intermediate-risk AML who received allo-SCT in CR1.[6]

In support of these findings, Gupta et al report a survival benefit for AML patients in CR1 with unfavorable cytogenetics with allo-SCT; most notably, there was no difference in outcome between MRD versus URD allo-SCT. This study also redemonstrates that older patients and patients receiving reduced-intensity conditioning (RIC) had an inferior outcome.[1] An aging population is increasing the proportion of persons susceptible to diseases for which SCT is indicated. However, with the median age of AML approaching 70 years, allo-SCT is not a treatment option for the majority of patients. Because relapse is the major cause of treatment failure after allo-SCT in patients with HR AML, new approaches to prevent disease recurrence are being explored. A question of practical importance is whether patients undergoing transplantation in CR1 will benefit from postremission chemotherapy before transplantation. There are no prospective studies demonstrating that any form of postremission chemotherapy further reduces the risk of posttransplantation relapse. However, results from 2 retrospective registry analyses suggest no benefit of adding further consolidation chemotherapy before allo-SCT; in both studies (transplant period 1980-mid 1990s), most patients were young and received full-intensity conditioning MRD allo-SCT.[7,8] In the study by Gupta et al, relapse occurred in 37% to 40% and was higher in patients receiving RIC regimens.[1] These findings highlight the importance of the depth-of-remission pre-SCT, especially in recipients of the RIC group. The role of postremission consolidation chemotherapy before RIC allo-SCT in HR AML has not been adequately addressed. Given that the majority of relapses occur within 1 year after transplantation, these patients should be enrolled in prospective studies to explore preemptive posttransplantation therapy to prevent early relapses. We speculate that, in the future, disease relapse may be further decreased by posttransplantation adjuvant therapies that could include chemotherapy (eg, azacitidine), leukemia vaccines, and adoptive transfer of natural killer cells or leukemia-specific T cells.

In patients with unfavorable cytogenetics in AML CR1, transplantation leads to improved long-term survival in the range of 34% to 42% versus less than 20% with nontransplantation therapy. Importantly, the outcome of transplantation appears to be comparable for recipients of URD versus MRD transplantation.[1,2] This is especially relevant in view of the fact that more than 20 000 allo-SCT procedures are performed annually throughout the world,[9] and more than half are from non-MSD stem cell sources. The analysis by Gupta et al was performed for the transplantation period 1995 to 2006.[1] With improvements in transplantation procedures including better donor selection (with high-resolution HLA typing), excellent supportive care, and preemptive therapy in high-risk patients, we anticipate that outcomes will continue to improve.

Currently, a stem cell source can be found for virtually all patients who have an indication to receive allo-SCT. Haploidentical-related donor or cord blood transplantations (CBT) have emerged as alternatives to fill the gap for those patients who do not have MSD or URD and the outcome of these types of transplantations is expected to be better than chemotherapy alone in high-risk AML CR1. The results of 4 comparative studies together with meta-analyses of CBT versus URD– bone marrow transplantation (BMT) showed that despite increased disparity, the results of CBT appear to be as promising as those of matched URD-BMT in adults with hematologic malignancies.[10] In the absence of an HLA-matched donor, both CBT and haploidentical-SCT strategies (center dependent) are suitable options to treat these HR patients.[11] An upcoming Blood and Marrow Transplant Clinical Trials Network study will compare haploidentical-SCT with CBT.

In summary, the current study provides insight into the applicability of expanding allo-SCT to all possible non-MRD stem cell sources to improve transplantation outcome in patients with AML in CR1 with unfavorable cytogenetics. While considering allo-SCT for AML in CR1, we need to make a judgment as to whether the relapse risk significantly exceeds the incremental mortality from allo-SCT over standard chemotherapy. The individual transplant center experience using URD, CBT, and haploidentical transplantation should also be taken into consideration. Enrollment in clinical trials should be encouraged, with the hope that the information from the current study will instigate studies evaluating various postremission strategies including CBT and haploidentical-SCT if no matched donor is available for HR AML CR1.

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

REFERENCES

1. Gupta V, Tallman MS, He W, et al. Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis. *Blood.* 2010;116(11):1839-1848.

2. Walter RB, Pagel JM, Gooley TA, et al. Comparison of matched unrelated and matched related donor myeloablative hematopoietic cell transplantation for adults with acute myeloid leukemia in first remission. *Leukemia.* 2010;24(7):1276-1282.

3. Rowe JM. Optimal induction and post-remission therapy for AML in first remission. *Hematology Am Soc Hematol Educ Program.* 2009;396-405.

4. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med.* 2008;358(18):1909-1918.

5. Dohner K, Dohner H. Molecular characterization of acute myeloid leukemia. *Haematologica.* 2008;93(7):976-982.

6. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA.* 2009;301(22):2349-2361.

7. Tallman MS, Rowlings PA, Milone G, et al. Effect of postremission chemotherapy before human leukocyte antigen-identical sibling transplantation for acute myelogenous leukemia in first complete remission. *Blood.* 2000;96(4):1254-1258.

8. Cahn JY, Labopin M, Sierra J, et al. No impact of high-dose cytarabine on the outcome of patients transplanted for acute myeloblastic leukaemia in first remission. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Br J Haematol.* 2000;110(2):308-314.

9. Gratwohl A, Baldomero H, Aljurf M, et al. Hematopoietic stem cell transplantation: a global perspective. *JAMA.* 2010;303(16):1617-1624.

10. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med.* 2004;351(22):2276-2285.

11. Hough R, Rocha V. Transplant outcomes in acute leukemia. II. *Semin Hematol.* 2010;47(1):51-58.