EDITORIAL

Myelodysplastic Syndrome After Autologous Transplantation for Lymphoma: The Price of Progress?

By Richard M. Stone

PROGRESS, IT SEEMS, never occurs without unintended or unwanted problems. For example, the internal combustion engine revolutionized transportation, but with it came highway fatalities, air pollution, and the strip mall. Must it be the same in medicine? Miller et al's description[1] of patients who developed myelodysplastic syndrome and/or acute leukemia after high-dose therapy and autologous hematopoietic stem cell rescue for lymphoma brings up the issue again. The short-term safety (<10% acute mortality) of autologous transplantation as a treatment modality for non-Hodgkin's lymphoma and Hodgkin's disease has been previously established.[2,3] Most importantly, patients with relapsed non-Hodgkin's lymphoma[2,4] and refractory Hodgkin's disease,[3,5] not generally considered curable with conventional salvage chemotherapy, may achieve long-term disease-free survival after undergoing transplantation. In patients who are selected on the basis of continued sensitivity of their tumors to chemotherapy and who have minimal residual disease before transplant, the long-term disease-free survival rate may be 40% to 50%.[2,4] The use of this expensive technology has clearly benefited many patients and could help a great many more in the future. The success of myeloablative therapy in this population has convinced many investigators to study the role of autologous transplantation in patients with non-Hodgkin's lymphoma in first remission who have low-grade disease or in those with intermediate- or high-grade disease at significant risk to relapse on the basis of advanced stage at presentation.[6-8] Therefore, the experience described by transplant physicians at the University of Minnesota[1] and preliminary reports from several other centers[9-11] concerning the development of myelodysplasia as a late complication after autologous transplantation mandates careful examination.

When one learns of a 15% actuarial incidence of myelodysplasia after autologous bone marrow transplantation,[1] many questions arise. Is the problem actually of such a significant magnitude or is this just an aberration at one center caused by one particular approach or by the inevitable vicissitudes of statistics (ie, bad luck)? Could it be an artifact caused by an inability to diagnose myelodysplasia as accurately after transplant as in the patient who walks in off the street, never having previously met a medical oncologist? Can we identify patients who are at particularly high risk to develop myelodysplasia after transplantation? Is myelodysplasia really a "complication" of transplant or is it just a consequence of successful antilymphoma therapy? More patients with lymphoma who have received many alkylating agent-containing chemotherapeutic regimens may now be long-term survivors. Should our approach to patients with advanced or poor prognosis lymphoma be altered based on this description of a potentially new setting for iatrogenic leukemia? And I've just begun to ask.

Myelodysplasia after autologous transplant for lymphoma, if not a real problem, is certainly being reported with increasing frequency. In addition to Miller et al,[1] two groups of investigators presented similar findings at the 1993 American Society of Hematology meeting[9,10] and the Nebraska group described their experience earlier the same year at ASCO.[11] Investigators from Paris wrote to the editor of the *Journal of Clinical Oncology* last year to describe 3 cases of secondary AML from a group of 68 autologous transplants for advanced Hodgkin's or non-Hodgkin's lymphoma.[12] In the current series,[1] the crude incidence of myelodysplasia was 9 of 206 (4%) of all transplanted patients. However, because of the confounding effect of therapy administered for posttransplant relapse, only 7 were considered in the calculation of the cumulative 5-year actuarial risk of myelodysplastic syndrome, which was 14.5% ± 14.7%. The 95% confidence interval is larger than the actual "incidence" because of the relatively few patients at risk many years after transplant and the relatively short length of median follow-up. It would have been helpful to know what the confidence interval for myelodysplastic syndrome development was at each time point after transplant. Despite the uncertainty in the number and the heterogeneity of the patient selection and preparative regimens, the projected cumulative incidence is surprisingly similar when compared with the 6% to 18% figures from recently reported abstracts (Table 1). These 5-year rates are also similar to the cumulative incidence of myelodysplastic syndrome/acute myeloid leukemia (AML) (approximately 7%) in the two large series that described this problem in non-Hodgkin's lymphoma patients exposed to prolonged alkylating agent therapy and/or low-dose radiation.[13,14] Although the risk of secondary leukemia after alkylating agent therapy for Hodgkin's disease is well known,[15] this complication has not been noted in patients with non-Hodgkin's lymphoma treated with aggressive CHOP-based regimens.[16,17]

What do these posttransplant patients with myelodysplasic syndrome really have? There can be little doubt about those with excess blasts and/or leukemia who eventually die as a consequence of bone marrow failure. These unfortunate individuals certainly have a clonal malignancy arising as a consequence of stem cell damage that results in a growth advantage for the progeny of the affected cells. In the current series,[1] only 3 patients presented with excess blasts in the marrow or blood; 1 of these 3 died 3 months after the diagnosis of myelodysplastic syndrome, whereas the other two were diagnosed just before the report was written. Two other patients died at 8 and 10 months after the diagnosis of apparent

Table 1. Myelodysplasia After Autologous Bone Marrow Transplantation for Lymphoma

Series	No. Transplanted	Cases of MDS + AML (crude incidence)	Actuarial Incidence	Time to MDS (pdx/ptx)
Nebraska[11]	117	4 (3%)	6.8% (5 yr)	NA/8-70
City of Hope[10]	275	8 + 2 (4%)*	6.4% (2 yr)	47/17
Dana-Farber[9]	262	18 + 2 (7%)	18% ± 9% (6 yr)	69/31
Minnesota[1]	206	8 + 1 (4%)	14.5% ± 11.6% (5 yr)	65/34

Abbreviations: NA, not available; pdx, months after diagnosis of lymphoma; ptx, months after transplant.

* Including 5 patients with cytogenetic abnormalities only.

refractory anemia. Because one of these developed bone marrow failure only 11 months after transplant and the other received etoposide, velban, and doxorubicin plus "extensive" radiation therapy for a posttransplant relapse, perhaps they just represented late autograft failure and not true myelodysplasia, although the former patient did convert to AML before his demise. In fact, 5 of these patients evidenced prolonged cytopenias after transplant. Marrow and peripheral blood exhibited dysplastic features in all myelodysplastic syndrome patients, but marrow examinations after transplant, even in those doing perfectly well clinically and hematologically, may be rich in morphologic dysplasia. Myelodysplasia after bone marrow transplant may not necessarily be a terrible disease. One of the Minnesota patients has been alive for almost 3 years with this diagnosis. On the other hand, whether disordered engraftment is the cause for what may be called myelodysplasia or represents a symptom of a novel clonal bone marrow stem cell disorder is a question of greater interest to semanticists than to patients who need transfusions.

To fully gauge the magnitude of the problem, much longer posttransplant follow-up and more clinical data concerning patients said to have developed posttransplant myelodysplastic syndrome are needed. The available cytogenetic data is similarly incomplete. In the current series,[1] all 6 evaluated patients had the kind of cytogenetics that one worries about in de novo myelodysplastic syndrome patients. On the other hand, 3 of these had a significant percentage of normal metaphases (including the 1 long-term myelodysplastic syndrome survivor). Furthermore, we do not know what results would be obtained if every patient had a bone marrow karyotype performed, say, 3 years after transplant. At the Dana-Farber Cancer Institute, we have found that 50% of sporadically tested posttransplant hematologically normal patients harbor clonal karyotypic abnormalities after transplant, even including monosomy 7. Nothing adverse has happened to some of these patients up to several years after such an ominous finding was discovered. To identify a patient as having myelodysplastic syndrome only on the basis of an abnormal karyotype (as was done by the City of Hope group)[10] is to use a paint roller when a small brush might be more appropriate. I bring these issues up not to lightly dismiss oncologist-produced gross chromosomal changes, but to merely call for careful scrutiny of these findings, and, though it is glib, for a great deal more prospective follow-up data.

Having raised a few cautionary notes about the actual numerical scope and nature of posttransplant myelodysplas-

tic syndrome, it is nonetheless quite appropriate to think about the potential cause of this putative problem. Most of the available evidence suggests that the pretransplant therapy, rather than the myeloablation, is the culprit. First, the 6-year interval from the time of initial therapy to myelodysplastic syndrome development[1] corresponds closely to the typical alkylating agent-related myelodysplastic syndrome incubation period in the nontransplant setting. It is virtually identical to the median time to myelodysplastic syndrome development in the National Cancer Institute and Danish studies in non-Hodgkin's lymphoma patients[13,14] and not dissimilar to the interval between treatment and secondary leukemia in Hodgkin's disease patients.[15] Second, the patients received a great deal of chemotherapy before coming to transplant. In addition to their original induction regimens, almost all received additional chemotherapy and/or radiotherapy to treat one or more relapses. It is possible that chronically abused bone marrow stem cells are more likely to undergo malignant transformation than those exposed relatively briefly to high-dose alkylating agent therapy.[16,17] Third, myelodysplasia rarely develops after allogeneic transplantation,[18] also suggesting that the infused marrow rather than residual damaged host cells gives rise to the myelodysplasia. If total body irradiation (TBI) is used in the transplant preparative regimen, it is unlikely that host stem cells will survive. Despite a suggestion by the Nebraska investigators[11] that patients receiving a preparative regimen including TBI are at higher risk for myelodysplastic syndrome, in the current series,[1] 5 of 9 patients were conditioned with chemotherapy alone. Nonetheless, to formally prove that the myelodysplastic clone arises from the autograft rather than surviving residual "host" marrow, it would be necessary to genetically mark (ie, with a retroviral vector) the graft[19] and eventually assay the myelodysplastic cells.

Without definitive evidence that the pretransplant antilymphoma therapy causes posttransplant myelodysplasia, one is left with searching for additional clues. One means to do this is to compare potential prognostic factors in patients who developed myelodysplasia with those who did not. When a univariate analysis is performed, we have found that those with a lower platelet count just before myeloablation, a longer interval between first antilymphoma therapy and transplant, a greater number of months on alkylating agents, exposure to radiation therapy, and a prior relapse were more likely to develop myelodysplastic syndrome.[9] Each of these features suggests that the pretransplant cytoreductive therapy is the etiology of the eventual myelodys-

plasia. Because these variables are unlikely to be independent, one would ideally perform logistic regression, but this statistical maneuver is hindered by the rarity of events (eg, 9 of 206 in the Miller series, 20 of 262 in the Dana-Farber patients). Any claims made on the basis of univariate analysis alone must be interpreted carefully. For example, Miller et al[1] state that if rescue was performed using peripheral blood stem cells (PBSC) the actuarial risk of myelodysplastic syndrome was 31% ± 33%, significantly greater than the 10.5% ± 12% risk if bone marrow was used. Many other potential selection features in these two groups could obscure the notion that PBSC are less "safe" than marrow when it comes to myelodysplasia.

Although the bulk of available data favors the pretransplant antilymphoma therapy as the etiology of post-transplant myelodysplastic syndrome, the transplant procedure itself may be an accomplice. First, 3 (all that were so analyzed) of the Minnesota myelodysplastic syndrome patients had normal cytogenetics at the time of their autologous harvest. The onset of the karyotypic abnormalities would have to be posttransplant in these cases. These autologous cells were never exposed to the high-dose conditioning regimen, so if they were the source of the eventual cytogenetic abnormalities (again assuming complete eradication of all endogenous bone marrow cells by the preparative regimen), perhaps the stress of re-engraftment or the presence of abnormal stromal elements caused this serious perturbation. In this model, the transplant procedure would play a synergistic role with all the previous alkylating agent therapy. Another cautionary note about exonerating the transplant itself is our observation that several patients with lymphoma transplanted in first remission have developed myelodysplastic syndrome and/or AML.[9] These patients received 6 to 8 cycles of CHOP, a regimen not known to be leukemogenic.[16,17] In addition to wondering about the role of the transplant procedure, one must also keep in mind the potential effect/relationship of antibody purging as well as the presence of lymphoma cells infiltrating the marrow. As such, it is unclear if information derived from studies concerning transplants for lymphoma patients will be applicable to the increasing number of solid tumor patients who will receive similar high-dose therapy.

Except for the caveat raised about problems in upfront patients, the conclusions in these new reports of post-autotransplant myelodysplasia in lymphoma patients are something like the following: (1) discuss myelodysplasia as a potential complication of autologous transplantation when obtaining informed consent for the transplant; (2) transplant patients earlier in the course of their disease; and (3) determine surrogate markers for incipient myelodysplastic syndrome development before transplant (eg, clonal hematopoiesis[20] or cytogenetic abnormalities[21]). If stem cell harvesting without disease contamination and long-term storage were simple issues, one could even consider banking normal stem cells at the time of the original diagnosis. Subgroups of patients with non-Hodgkin's lymphoma can be predicted to do worse than others based on factors that suggest high volume disease.[22] However, even if first remission transplants were restricted to the poorest prognosis group, some

would receive this expensive and dangerous therapy who would have been cured with standard chemotherapy. Especially given the concern about long-term complications, more documentation of the efficacy of upfront transplant, especially relative to other nontransplant high-dose approaches, will be required.

The chief use of autologous transplantation in lymphoma will continue to be for the relapsed patient who has been rendered into a second partial or complete remission. There are no other equally efficacious alternative options for these patients, who would otherwise die. Selecting patients who are most likely to benefit from this procedure is still very important. Transplantation, even with a 10% long-term complication rate, is a rational choice. After I presented the Dana-Farber results at the ASH meeting in St Louis, a man came up after the session to ask a question. "Where do I fit in your data?" When he saw my startled look, he explained that he was a physician who contracted intermediate-grade lymphoma, had relapsed twice, was rendered into a minimal residual disease state, and then received (7 years ago) infusion of his previously harvested, anti-CD20–purged marrow followed by high-dose cyclophosphamide/TBI preparation. His lymphoma continues to be in remission, his blood counts are normal (although his most recent karyotype did show a clonal abnormality), and he is enjoying life and work. I asked about his reaction to the data in my presentation. "You should definitely study this issue further, but for patients like me with relapsed lymphoma, autologous transplantation is the best game in town; the procedure saved my life."

In addition to MOPP for Hodgkin's disease, chlorambucil for polycythemia vera, L-PAM for ovarian cancer, teniposide for childhood acute lymphocytic leukemia, and chronic cyclophosphamide for non-Hodgkin's lymphoma,[23] a new modality, autologous transplantation for lymphoma, is now associated with secondary myelodysplastic syndrome/AML. This problem may be a consequence, rather than a complication, of the myeloablative approach. The transplant procedure itself, while possibly playing a role, may not be as important as the pretransplant chemotherapy in causing this complication. We need more information about incidence, natural history, and etiology of postautologous transplant-associated myelodysplastic syndrome before our current therapeutic approaches can be rationally altered. Moreover, for certain patients, transplantation remains indispensable. In other words, we cannot stop using the car, but we should try to reduce our toxic emissions and drive as safely as possible.

REFERENCES

1. Miller JS, Arthur DC, Litz CE, Neglia JP, Miller WJ, Weisdorf DJ: Myelodysplastic syndrome after autologous bone marrow transplantation: An additional late complication of curative cancer therapy. Blood 83:3780, 1994

2. Freedman AS, Takvorian T, Anderson KC, Mauch P, Rabinowe SN, Blake K, Yeap B, Soiffer R, Coral F, Heflin L, Ritz J, Nadler LM: Autologous bone marrow transplantation in B-cell non-Hodgkin's lymphoma: Very low treatment-related mortality in 100 patients in sensitive relapse. J Clin Oncol 8:784, 1990

3. Chopra R, McMillan AK, Linch DC, Yuklea S, Taghipour G, Pearce R, Patterson KG, Goldstone AH: The place of high-dose

BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease. A single-center eight-year study of 155 patients. Blood 81:1137, 1993

4. Philip T, Armitage JO, Spitzer G, Chauvin F, Jagannath S, Cahn J-Y, Colombat P, Maraninchi D, Pico J, Besly A, Anderson C, Schots R, Biran P, Cabanillas F, Dicke K: High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate grade or high-grade non-Hodgkin's lymphoma. N Engl J Med 316:1493, 1987

5. Armitage JO: Bone marrow transplantation in the treatment of patients with lymphoma. Blood 73:1749, 1989

6. Freedman AS, Ritz J, Neuberg D, Anderson KC, Rabinowe SN, Mauch P, Takvorian T, Soiffer R, Blake K, Yeap B, Coral F, Nadler LM: Autologous bone marrow transplantation in 69 patients with a history of low-grade B-cell non-Hodgkin's lymphoma. Blood 77:2524, 1991

7. Nademanee A, Schmidt GM, O'Donnell MR, Snyder DS, Parker PA, Stein A, Smith E, Lipsett JA, Sniecinski I, Margolin K, Somlo G, Niland JC, Blume KG, Forman SJ: High-dose chemoradiotherapy followed by autologous bone marrow transplantation as consolidation therapy during first complete remission in adult patients with poor-risk aggressive lymphoma: A pilot study. Blood 80:1130, 1992

8. Freedman AS, Takvorian T, Neuberg D, Mauch P, Rabinowe SN, Anderson KC, Soiffer RJ, Spector N, Grossbard M, Robertson MJ, Blake K, Coral F, Canellos GP, Ritz J, Nadler LM: Autologous bone marrow transplantation in poor-prognosis intermediate-grade and high-grade B-cell non-Hodgkin's lymphoma in first remission: A pilot study. J Clin Oncol 11:931, 1993

9. Stone R, Neuberg D, Soiffer R, Whelan M, Leavitt P, Aster J, Takvorian R, Rabinowe S, Ritz J, Freedman A, Nadler L: Myelodysplastic syndrome (MDS) as a complication after autologous bone marrow transplantation (ABMT) for non-Hodgkin's lymphoma (NHL). Blood 82:196a, 1993 (abstr, suppl 1)

10. Traweek ST, Slovak ML, Nademanee AP, Byrnes RK, Niland JC, Forman SJ: Myelodysplastia occurring after autologous bone marrow transplantation (ABMT) for Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Blood 82:455a, 1993 (abstr, suppl 1)

11. Armitage J, Vose J, Anderson J, Bierman P, Bishop M, Kessinger A: Complete remission (CR) following high-dose chemotherapy (HDC) and autologous hematopoietic rescue for non-Hodgkin's lymphoma (NHL): Evaluation of CR durability and incidence of secondary myelodysplastic syndrome. Proc Am Soc Clin Oncol 12:363a, 1993

12. Marolleau JP, Brice P, Morel P, Gisselbrecht C: Secondary acute myeloid leukemia after autologous bone marrow transplantation for malignant lymphoma. J Clin Oncol 11:590, 1993

13. Greene NH, Young RC, Merrill JM, DeVita VT: Evidence of a treatment of dose response in acute nonlymphocytic leukemias which occur after therapy of non-Hodgkin's lymphoma. Cancer Res 43:1891, 1983

14. Pederson-Bjergaard J, Ersboll J, Sorensen HM, Keiding N, Larsen SO, Philip B, Larsen MS, Schultz H, Nissen NI: Risk of acute non-lymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. Ann Intern Med 103:195, 1985

15. Valagussa P, Santoro A, Fossati-Bellani F, Banfi A, Bonadonna G: Second acute leukemia and other malignancies following treatment for Hodgkin's disease. J Clin Oncol 4:820, 1986

16. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA Jr, Miller TP: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced Non-Hodgkin's lymphoma. N Engl J Med 328:1002, 1993

17. Shipp MA, Harrington DP, Klatt MM, Shipp MA, Harrington DP, Klatt MM, Jochelson MS, Pinkus GS, Marshall JL, Rosenthal DS, Skarin AT, Canellos GP: Identification of major prognostic subgroups of patients with large-cell lymphoma treated with m-BACOD or M-BACOD. Ann Intern Med 104:757, 1986

18. Witherspoon RP, Fisher LD, Schoch G, Martin P, Sullivan KM, Sanders J, Deeg HJ, Doney K, Thomas D, Storb R, Thomas ED: Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. N Engl J Med 321:784, 1989

19. Rill DR, Holladay MS, Heslop HE, Moen RC, Buschle M, Krance RA, Anderson WF, Ihle JN, Brenner MK: The contribution of autologous marrow infusion to the restoration of long-term hemopoiesis in cancer patients: a study using gene marking. Blood 82:86a, 1993 (abstr, suppl 1)

20. Busque L, Maragh M, DeHart D, McGanigle C, Vose J, Armitage J, Meisinger D, Wheeler C, Gaines L, Belanger R, Habel F, Dunbar C, Champagne M, Gross W, Weinstein H, Antin JH, Gilliland DG: Clonality of bone marrow repopulation after allogeneic and autologous bone marrow transplantation (ABMT). Blood 82:457a, 1993 (abstr, suppl 1)

21. Chao NJ, Nademanee AP, Long GD, Schmidt GM, Donlon TA, Parker P, Slovak ML, Nadasawa LS, Blume KG, Forman SJ: Importance of bone marrow cytogenetic evaluation before autologous bone marrow transplantation for hodgkin's disease. J Clin Oncol 9:1575, 1991

22. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: Predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987, 1993

23. Levine EG, Bloomfield CD: Leukemias and myelodysplastic syndromes secondary to drug, radiation, and environmental exposure. Semin Oncol 19:47, 1992