



Transplantation in Lymphoma

James O. Armitage

Since its inception, bone marrow transplantation has been an obvious treatment to test for patients with lymphoma. Lymphoma is a chemotherapy-sensitive malignancy in which escalating the doses of treatment might be expected to increase the cure rate. However, the first cure of lymphoma using high-dose therapy and autologous bone marrow transplantation was not reported until 1978.¹ Over the ensuing decade, many of the problems involved in autologous transplantation for patients with lymphoma were resolved, and high-dose therapy and hematopoietic stem cell transplantation using either bone marrow or blood derived cells has become a common treatment.

Allogeneic bone marrow transplantation has only more recently been applied in significant numbers to patients with lymphoma. The fact that most patients with lymphoma are not young and that the risk of treatment-related mortality is fairly high has limited the application of this treatment approach. However, the fact that relapses with certain types of lymphoma following bone marrow transplantation are frequent has led to a reevaluation of this treatment approach.

Early Clinical Trials

When it became apparent that bone marrow transplantation could be performed with reasonable safety, clinical trials of its use in specific lymphoma subtypes were instituted. Initially, transplant trials were in patients who had failed standard therapy and often had very advanced disease. However, in interpreting transplant trials, it is important to remember that transplant patients are generally younger than the median age for all patients with the particular type of lymphoma, and patients coming to transplant are less likely to have bone marrow involvement. The disease-free survival for patients with relapsed Hodgkin's disease undergoing autologous bone marrow transplantation has ranged from 20 to 60%.²⁻²¹ However, the chances for failure-free survival in most series was dependent upon the extent of previous therapy. Patients who come to transplantation earlier have a better chance for disease-free survival. Presumably, this is related, at least in part, to a lower level of chemotherapy resistance in the tumor.

The type of lymphoma most frequently treated with autologous bone marrow transplantation has been diffuse large-cell lymphoma.²²⁻³⁵ An early report of 100 patients

who underwent autologous bone marrow transplantation demonstrated that the treatment outcome was highly correlated to the tumor's responsiveness to chemotherapy administered previously.²² For chemotherapy sensitive relapse, approximately 35–40% of patients can achieve prolonged disease-free survival and apparent cure.

The results of trials in patients with follicular lymphoma have been less clear. In this disorder, the indolent natural history characterized by frequent and often long remissions followed by relapse has made physicians slower to carry out trials of transplantation. It also makes the interpretation of transplant trials more difficult. However, in recent years, a large number of patients treated in trials at St. Bartholomew's Hospital in London, the Dana-Farber Center in Boston, Stanford University, the University of Nebraska Medical Center, and other centers have demonstrated that prolonged disease-free survival can be seen in some patients and that the chances to benefit from therapy are, once again, related to the extent of previous chemotherapy.^{17,35-42}

The results of these studies of bone marrow transplantation in patients with lymphoma have demonstrated several general points. One of these is that the high-dose therapy that is the "treatment" in autologous bone marrow transplantation represents a more intensive but related form of treatment to what is considered standard therapy. Thus, it should not be surprising that the prognostic factors identified for transplantation are the same ones seen in clinical trials of standard dose therapy. Unfortunately, the relative merits of the commonly used high-dose therapy regimens are not clear. It is possible that total-body radiotherapy versus chemotherapy-only regimens, or different chemotherapy-only, high-dose regimens, would benefit different subgroups of patients. However, comparative trials have not been completed to address these issues.

A second issue that has become clear is that patients who benefit from transplantation generally do not have long-term complications related to the procedure. In a series of patients treated at the University of Nebraska Medical Center, the most frequent late complications related to specific organ dysfunction were hypothyroidism in 16% of the patients and cataracts in 6%.⁴³ However, the patients with hypothyroidism often had mantle radiotherapy before they came to transplantation. Approximately 90% of the trans-

planted patients returned full time to their previous occupation. However, approximately 40% of patients complained of alterations in sexual function. Late infectious complications were seen most often if the lymphoma relapsed, but herpes zoster was a frequent complication after discontinuing acyclovir, seen approximately 24% of the time.

The late complication after transplantation of most concern is the development of secondary malignancies due to the therapy. To date, there has been no obvious increase in the incidence of solid tumors, although the duration of follow-up might not be sufficient to identify such a trend. However, there is an apparent increase in acute leukemia and/or myelodysplastic syndrome in patients undergoing autotransplantation for lymphoma with total body radiation administered in the preparative regimen.⁴⁴⁻⁴⁸ Unlike the situation with Hodgkin's disease, acute leukemia or myelodysplasia is an unusual complication in the treatment of patients with follicular lymphoma. The risk of development of this complication in patients more than 40 years of age seems greater than 10%.

Throughout trials for non-Hodgkin's lymphomas and Hodgkin's disease, the most common type of transplant performed used autologous cells derived from the bone marrow or blood. Increasingly, transplants with both blood-derived cells have surpassed the number of transplants using bone marrow-derived cells. Allogeneic transplants using either blood or bone marrow have been performed less frequently because of the comparatively older age of most lymphoma patients and the absence of donors for the majority of patients.⁴⁹⁻⁵⁵ However, the net result of allogeneic transplantation in lymphoma has been comparable to that seen with autotransplantation, despite a higher mortality rate. There appears to be an antilymphoma effect of allogeneic cells.⁴⁹ If sufficient donors could be found and the complications of graft-versus-host disease ameliorated without eliminating the apparent antilymphoma effect of allogeneic transplantation, it would probably become the treatment of choice.

Comparative Trials

The most convincing evidence for the efficacy of high-dose therapy and autotransplantation management of patients with lymphomas would be from comparative or Phase III trials. These have recently been initiated in some but not all subtypes of lymphomas. Randomized trials testing the relative merits of high-dose therapy with autotransplantation versus standard-dose therapy could be performed at several points in the course of the disease. Patients could have high-dose therapy and autotransplantation incorporated into the planned initial therapy, patients might only be treated if they responded slowly to the initial standard-dose therapy, the transplantation could be used as an adjuvant treatment (i.e., in a manner analogous to chemotherapy use in primary breast cancer) in complete responders, or the high-dose therapy might be used as a salvage treatment.

The diseases most tested by Phase III trials to determine the place of autotransplantation in the management of

patients with lymphoma are the diffuse aggressive lymphomas typified by diffuse large-cell lymphoma. Here single-arm studies of early incorporation of autotransplantation have been encouraging.⁵⁶⁻⁶³ In the aggressive lymphomas, each of the strategies for the use of high-dose therapy has been tested. An important trial of the use of high-dose therapy versus standard-dose therapy as salvage treatment for patients with relapsed but chemotherapy-sensitive diffuse aggressive lymphoma was reported recently.⁶⁴ After demonstrating responsiveness to DHAP (dexamethasone, cytarabine and cisplatin), 109 patients were randomized to continue DHAP in standard doses or to undergo autotransplantation using the BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) regimen. Fifty-four patients continued with standard-dose DHAP, and 55 patients were randomized to transplantation. The event-free survival (12% versus 46%, $P = 0.001$) and the overall survival (32% versus 53%, $P = 0.04$) favored autotransplantation. This is in spite of the fact that patients who failed DHAP were offered autotransplantation. Some patients were unable to undergo salvage transplantation, and even when patients could receive the transplant, their response rate was poorer than when it was done earlier.

A trial of adjuvant bone marrow transplantation compared to traditional dose-consolidative therapy in patients who have achieved initial complete remission was carried out in France by the Groupe d'Etude des Lymphomes de l'Adult.⁶⁵ After achieving a complete remission with the ACVBP (Adriamycin, cyclophosphamide, vindesine, bleomycin, and prednisone) regimen, 464 patients were randomized to receive consolidative therapy with ifosfamide, etoposide, L-asparaginase, and cytarabine or to undergo autotransplantation with CVB (cyclophosphamide, etoposide, and bleomycin). The disease-free survival for all patients randomized slightly, but not sufficiently, and favored bone marrow transplantation. However, when patients were stratified using the International Prognostic Index, those with intermediate and high risk factors had significantly better disease-free survival if they underwent transplantation.

Two studies have been completed testing autotransplantation versus standard-dose chemotherapy in patients who did not achieve a prompt remission to a front-line chemotherapy regimen. In Italy, 51 patients who had not achieved rapid remission to either MACOP-B (methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin) or F-MACHOP (fluorouracil, methotrexate, cytarabine, cyclophosphamide, Adriamycin, vincristine, and prednisone) were randomly allocated to DHAP or autotransplantation.⁶⁶ In Holland, 69 patients who have failed to achieve rapid complete remission to CHOP were allocated to continuing CHOP or to undergo autotransplantation.⁶⁷ In neither series was there a significant advantage to the patients undergoing transplantation.

The Tumor Institute in Milan, Italy compared high doses of single chemotherapeutic agents followed by autotransplantation versus MACOP-B as the initial treatment for patients with diffuse aggressive B-cell lymphomas with high-

risk characteristics.⁶⁸ Autotransplant patients demonstrated a superior failure-free survival (78% versus 33%, $P < 0.001$), and there was a trend for overall survival favoring the autotransplant patients. Once again, patients were offered autotransplant if they failed the initial chemotherapy regimen, but all such patients were not able to undergo the treatment, and the results with autotransplantation appeared inferior after failing the primary chemotherapy regimen.

More recent trials seem to confirm these results. It appears that bone marrow transplantation can substitute for several cycles of chemotherapy. However, to see the maximum benefit up-front, transplantation needs to be used as a "adjuvant" therapy after the completion of a standard dose of chemotherapy in high-risk patients.

A randomized trial of autotransplantation in the management of patients with Hodgkin's disease was carried out in the United Kingdom by Linch et al.⁶⁹ Forty patients with relapsed or refractory Hodgkin's disease were randomly allocated to receive autotransplantation with the BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen or to receive the same agents at lower doses not requiring hematopoietic stem cell support. Because of a highly significant failure-free survival in favor of the autotransplant patients, the study was terminated with only 20 patients in each arm. The overall survival between the two groups was not significant. There has been no comparative trial of early transplantation in Hodgkin's disease, but one Phase II trial was encouraging.⁷⁰

There has been no completed Phase III trial reported comparing high-dose therapy and autotransplantation versus standard-dose therapy in patients with low-grade lymphomas. A retrospective comparison of patients with follicular lymphoma in second remission treated with cyclophosphamide plus total-body radiotherapy and autotransplantation versus historical control patients has been reported from St. Bartholomew Hospital in London.⁷¹ In this case, there was a significant failure-free survival advantage in favor of autotransplantation, but the overall survival did not vary.

Conclusion

Although there are several bits of data suggesting that autotransplantation is a superior therapy for certain subgroups of patients with lymphoma, it is still clearly an imperfect approach. The major reason for failure continues to be lymphoma relapse. A number of new approaches are being tested to overcome this problem. These include new drugs and/or better ways to use radiotherapy. For example, radiolabeled antibodies provide a potential approach to deliver high doses of radiotherapy without undue toxicity.^{72,73} Numerous approaches to the use of adjuvant immunotherapy in patients undergoing transplantation are being tested. These include tumor vaccines to stimulate the redevelopment of the immune system after transplantation and chemicals to cause immune stimulation.⁷⁴ However, it is worth remembering that allogeneic bone marrow transplantation is a way to provide cellular immunotherapy.

Finally, the most obvious way to improve the results of

transplantation today would be to use the treatment early in the course of the disease. At the present time, less than half of patients who are potential candidates for autotransplantation for the management of lymphoma actually receive the treatment. Although this is because of patient reluctance in some cases and insurance problems in others, the major impediment is probably physicians not recommending this treatment to their patients at an appropriate time in the course of the disease. The most obvious way to improve the results would be to make the treatment available to patients at the first evidence that their disease is not likely to be cured with standard-dose therapy.

References

1. Appelbaum FR, Herzig GP, Ziegler JL, Graw RG, Levine AS, and Deisseroth AB: Successful engraftment of cryopreserved autologous bone marrow in patients with malignant lymphoma. *Blood* 1978; 52:85-95.
2. Jagannath S, Dicke KA, Armitage JO, Cabanillas FF, Horwitz LJ, Vellekoop L, Zander AR, and Spitzer G: High-dose cyclophosphamide, carmustine, and etoposide and autologous bone marrow transplantation for relapsed Hodgkin's disease. *Ann. Intern. Med.* 1986; 104:163-168.
3. Carella AM, Congiu AM, Gaozza E, Mazza P, Ricci P, Visani G, Meloni G, Cimino G, Mangoni L, Coser P, Luigi Cetto G, Cimino R, Alessandrino EP, Brusamolino E, Santini G, Tura S, Mandelli F, Rizzoli V, Bernasconi C, and Marmont AM: High-dose chemotherapy with autologous bone marrow transplantation in 50 advanced resistant Hodgkin's disease patients: an Italian study group report. *J. Clin. Oncol.* 1988; 6:1411-1416.
4. Gribben JG, Linch DC, Singer CRG, McMillan AK, Jarrett M, and Goldstone AH: Successful treatment of refractory Hodgkin's disease by high-dose combination chemotherapy and autologous bone marrow transplantation. *Blood* 1989; 73:340-344.
5. Armitage JO, Bierman PJ, Vose JM, Anderson JR, Weisenburger DD, Kessinger A, Reed EC, Vaughan WP, Coccia PF, and Purtilo DT: Autologous bone marrow transplantation for patients with relapsed Hodgkin's disease. *Am. J. Med.* 1991; 91:605-611.
6. Horning SJ, Negrin RS, Chao NJ, Long GD, Hoppe RT, and Blume KG: Fractionated total-body irradiation, etoposide, and cyclophosphamide plus autografting in Hodgkin's disease and non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1994; 12:2552-2558.
7. Phillips GL, Wolff SN, Herzig RH, Lazarus HM, Fay JW, Lin HS, Shina DC, Glasgow GP, Griffith RC, Lamb CW, and Herzig GP: Treatment of progressive Hodgkin's disease with intensive chemoradiotherapy and autologous bone marrow transplantation. *Blood* 1989; 73:2086-2092.
8. Reece DE, Barnett MJ, Connors JM, Fairey RN, Greer JP, Herzig GP, Herzig RH, Klingemann HG, O'Reilly SE, Shepherd JD, Spinelli JJ, Voss NJ, Wolff SN, and Phillips GL: Intensive chemotherapy with cyclophosphamide, carmustine, and etoposide followed by autologous bone marrow transplantation for relapsed Hodgkin's disease. *J. Clin. Oncol.* 1991; 9:1871-1879.
9. Crump M, Smith AM, Brandwein J, Couture F, Sherret H, Sutton DMC, Scott JG, McCrae J, Murray C, Pantalony D, Sutcliffe SB, and Keating A: High-dose etoposide and melphalan, and autologous bone marrow transplantation for

- patients with advanced Hodgkin's disease. Importance of disease status at transplant. *J. Clin. Oncol.* 1993; 1:704-711.
10. Gianni AM, Siena S, Bregni M, Lombardi F, Gandola L, Di Nicola M, Magni M, Peccatori F, Valagussa P, and Bonadonna G: High-dose sequential chemo-radiotherapy with peripheral blood progenitor cell support the relapsed or refractory Hodgkin's disease—a 6-year update. *Ann. Oncol.* 1993; 4:889-891.
 11. Yahalom J, Gulati SC, Toia M, Maslak P, McCarron EG, O'Brien JP, Portlock CS, Straus DJ, Phillips J, and Fuks Z: Accelerated hyperfractionated total-lymphoid irradiation, high-dose chemotherapy, and autologous bone marrow transplantation for refractory and relapsing patients with Hodgkin's disease. *J. Clin. Oncol.* 1993; 6:1062-1070.
 12. Reece DE, Connors JM, Spinelli JJ, Barnett MJ, Fairey RN, Klingemann HG, Natel SH, O'Reilly S, Shepherd JD, Sutherland HJ, Voss N, Chan KW, and Phillips GL: Intensive therapy with cyclophosphamide, carmustine, etoposide \pm cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy. *Blood* 1994; 83:1193-1199.
 13. Chopra R, McMillan AK, Linch DC, Yuklea S, Taghipour G, Pearce R, Patterson KG, and 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* 1993; 81:1137-1145.
 14. Bierman PJ, Bagin RG, Jagannath S, Vose JM, Spitzer G, Kessinger A, Dicke KA, and Armitage JO: High-dose chemotherapy followed by autologous hematopoietic rescue in Hodgkin's disease. Long term follow-up in 128 patients. *Ann. Oncol.* 1993; 4:767-773.
 15. Nademanee A, O'Donnell MR, Snyder DS, Schmidt GM, Parker PM, Stein AS, Smith EP, Molina A, Stepan DE, Somolo G, Margolin KA, Sniecinski I, Dajis AC, Niland J, Pezner R, and Forman SJ: High-dose chemotherapy with or without total body irradiation followed by autologous bone marrow and/or peripheral blood stem cell transplantation for patients with relapsed and refractory Hodgkin's disease. Results in 85 patients with analysis of prognostic factors. *Blood* 1995; 85:1381-1390.
 16. Burns LJ, Daniels KA, McGlave PB, Miller WJ, Ramsay NKC, Kersey JH, and Weisdorf DJ: Autologous stem cell transplantation for refractory and relapsed Hodgkin's disease: factors predictive of prolonged survival. *Bone Marrow Transplant.* 1995; 16:13-18.
 17. Jagannath S, Armitage JO, Dicke DA, Tucker SL, Velasquez W, Smith K, Vaughan WP, Kessinger A, Horwitz LJ, Hagemester FB, McLaughlin P, Cabanilla F, and Spitzer G: Prognostic factors for response and survival after high-dose cyclophosphamide, carmustine, and etoposide with autologous bone marrow transplantation for relapsed Hodgkin's disease. *J. Clin. Oncol.* 1989; 7:179-185.
 18. Bierman PJ, Anderson JR, Freeman MB, Vose JM, Kessinger A, Bishop MR, and Armitage JO: High-dose chemotherapy followed by autologous hematopoietic rescue for Hodgkin's disease patients following first relapse after chemotherapy. *Ann. Oncol.* 1996; 7:151-156.
 19. Spinolo JA, Jagannath S, Velasquez W, Spitzer G, Cabanillas F, Hagemester F, Horwitz LJ, and Dicke KA: Cisplatin-CBV with autologous bone marrow transplantation for relapsed Hodgkin's disease. *Leuk. Lymphoma* 1993; 9:71-77.
 20. Moormeier JA, Williams SF, Kammer LS, Ellis ED, Garner M, Farah R, Weichselbaum RR, and Bitran JD: Autologous bone marrow transplantation followed by involved field radiotherapy in patients with relapsed or refractory Hodgkin's disease. *Leuk. Lymphoma* 1991; 5:243-248.
 21. Reece DR, Barnett MJ, Shepherd JD, Hogge DE, Klasa RJ, Natel SH, Sutherland HJ, Klingemann HG, Fairey RN, Voss NJ, Connors JM, O'Reilly SE, Spinelli JJ, and Phillips GL: High-dose cyclophosphamide, carmustine (BCNU), and etoposide (VP16-213) with or without cisplatin (CBV \pm P) and autologous transplantation for patients with Hodgkin's disease who fail to enter a complete remission after combination chemotherapy. *Blood* 1995; 86:451-456.
 22. Philip T, Armitage JO, Spitzer G, Chauvin F, Jagannath S, Cahn JY, Colombat P, Goldstone AH, Gorin NC, Flesh M, Laporte JP, Maraninchi D, Pico JL, Bosly A, Anderson C, Schots R, Biron P, Cabanillas R, and 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.* 1987; 316:1493-1498.
 23. Colombat P, Gorin NC, Lemonnier MP, Binet C, Laporte JP, Douay L, Desbois I, Lopez M, Lamagnere JP, and Najman A: The role of autologous bone marrow transplantation in 46 adult patients with non-Hodgkin's lymphomas. *J. Clin. Oncol.* 1990; 8:630-637.
 24. Phillips GL, Fay JW, Herzig RH, Lazarus HM, Wolff SN, Lins HS, Shina DC, Glasgow GP, Griffith RC, Lamb CW, and Herzig GP: The treatment of progressive non-Hodgkin's lymphoma with intensive chemoradiotherapy and autologous marrow transplantation. *Blood* 1990; 75:831-838.
 25. Petersen FB, Appelbaum FR, Hill R, Fisher LD, Bigelow CL, Sanders JE, Sullivan KM, Bensinger WI, Witherspoon RP, Storb R, Clift RA, Fefer A, Press OW, Weiden PL, Singer J, Thomas ED, and Buckner CD: Autologous marrow transplantation for malignant lymphoma. A report of 101 cases from Seattle. *J. Clin. Oncol.* 1990; 8:638-647.
 26. Weisdorf DJ, Haake R, Miller WJ, McGlave PB, LeBien TW, Valleria DA, Lasky LC, Kim TH, Peterson BA, Ramsay NKC, Kersey JA, and Hurd DD: Autologous bone marrow transplantation for progressive non-Hodgkin's lymphoma: clinical impact of immunophenotype and in vitro purging. *Bone Marrow Transplant* 1991; 8:135-142.
 27. Lazarus HM, Crilley P, Ciobanu N, Creger RJ, Fox RM, Shina DC, Bulova SI, Gucalp R, Cooper BW, Topolsky D, Soegiarso W, and Brodsky I: High-dose carmustine, etoposide, and cisplatin and autologous bone marrow transplantation for relapsed and refractory lymphoma. *J. Clin. Oncol.* 1992; 10:1682-1689.
 28. Gulati S, Yahalom J, Acaba L, Reich L, Motzer R, Crown J, Toia M, Igarashi T, Lemoli R, Hanninen E, and Doherty M: Treatment of patients with relapsed and resistant non-Hodgkin's lymphoma using total body irradiation, etoposide, and cyclophosphamide and autologous bone marrow transplantation. *J. Clin. Oncol.* 1992; 10:936-941.
 29. Vose JM, Anderson JR, Kessinger A, Bierman PJ, Coccia P, Reed EC, Gordon B, and Armitage JO: High-dose chemotherapy and autologous hematopoietic stem-cell transplantation for aggressive non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1993; 11:1846-1851.
 30. Rapoport AP, Rowe JM, Kouides PA, Duerst RA, Abboud CN, Leisveld JL, Packman CH, Eberly S, Sherman M, Tanner MA, Constine LS, and DiPersio JF: One hundred autotransplants for relapsed or refractory Hodgkin's disease

- and lymphoma. Value of pretransplant disease status for predicting outcome. *J. Clin. Oncol.* 1993; 11:2341-2361.
31. Wheeler C, Strawderman M, Ayash L, Hollowell Churchill W, Bierer BE, Elias A, Gililand DG, Antman K, Guinan EC, Eder JP, Weinstein H, Schwartz G, Ferrara J, Mazanet R, Rimm JJ, Tepler I, McCarthy P, Mauch P, Ault K, Gaynes L, McCauley M, Schnipper LE, and Antin J: Prognostic factors for treatment outcome in autotransplantation of intermediate-grade and high-grade non-Hodgkin's lymphoma with cyclophosphamide, carmustine, and etoposide. *J. Clin. Oncol.* 1993; 11:1085-1091.
 32. Weaver CH, Petersen FB, Appelbaum FR, Bensinger WI, Press O, Martin P, Sandmaier B, Deeg HJ, Hansen JA, Brunvand M, Rowley S, Benyunes K, Chauncey T, Fefer A, Hackman R, Gooley T, Schiffman K, Storb R, Sullivan KM, Weiden P, Witherpoon R, and Buckner CD: High-dose fractionated total-body irradiation, etoposide, and cyclophosphamide followed by autologous stem-cell support in patients with malignant lymphoma. *J. Clin. Oncol.* 1994; 12:2559-2566.
 33. van Besien K, Tabocoff J, Rodriquez M, Andersson B, Mehra R, Przepiorka D, Dimopoulos M, Giralt S, Suki S, Khouri I, Spitzer G, Jagannath S, Dicke K, Le Maistre CF, Deisseroth A, Cabanillas F, and Champlin RE: High-dose chemotherapy with BEAC regimen and autologous bone marrow transplantation for intermediate grade and immunoblastic lymphoma: durable complete remission, but a high rate of regimen-related toxicity. *Bone Marrow Transplant.* 1995; 15:549-555.
 34. Mills W, Chopra R, McMillan A, Pearce R, Linch DC, and Goldstone AH: BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1995; 13:588-595.
 35. Bosly A, Coiffier B, Gisselbrecht C, Tilly H, Auzanneau G, Andrien F, Herbrecht R, Legros M, Devaux Y, Jaubert J, Pignon B, Michaux JL, Humblet Y, Dupriez B, Thyss A, and Lederlin P: Bone marrow transplantation prolongs survival after relapse in aggressive-lymphoma patients treated with the LNH-84 regimen. *J. Clin. Oncol.* 1992; 10:1615-1623.
 36. Colombat P, Donadio D, Fouillard L, Milpied N, Tilly H, Pico J, Abgrall JF, Coiffier B, Herbrecht R, and Phillip T: Value of autologous bone marrow transplantation in follicular lymphoma: a France Autogreffe retrospective study of 42 patients. *Bone Marrow Transplant.* 1994; 13:157-162.
 37. Schouten HC, Colombat P, Verdonck LF, Gorin NC, Bjorkstrand B, Taghipour G, and Goldstone AH: Autologous bone marrow transplantation for low-grade non-Hodgkin's lymphoma. The European Bone Marrow Transplant Group Experience. *Ann. Oncol.* 1994; 5 (Suppl. 2):S147-S149.
 38. Freedman AS, Ritz J, and Neuberg D: Autologous bone marrow transplantation in 69 patients with a history of low-grade B-cell non-Hodgkin's lymphoma. *Blood* 1991; 77:2524-2529.
 39. Bastion Y, Price P, Haioun C, Sonet A, Salles G, Marolleau JP, Espinouse D, Reyes F, Gisselbrecht C, and Coiffier B: Intensive therapy with peripheral blood progenitor cell transplantation in 60 patients with poor-prognosis follicular lymphoma. *Blood* 1995; 86:3257-3262.
 40. Haas R, Moos M, Karcher A, Mohle R, Witt B, Goldschmidt H, Fruhauf S, Flentje M, Wannenmacher M, and Hunstein W: Sequential high-dose therapy with peripheral-blood progenitor-cell support in low-grade non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1994; 12:1685-1692.
 41. Vose J, Rowlings PA, Lazarus HM, Phillips GL, Armitage JO, and Horowitz MM: High-dose therapy with autologous hematopoietic rescue for follicular non-Hodgkin's lymphoma. *Proc. Am. Soc. Clin. Oncol.* 1996; 15:1272.
 42. Schouten HC, Bierman PJ, Vaughan WP, Kessinger A, Vose JM, Weisenburger DD, and Armitage JO: Autologous bone marrow transplantation in follicular non-Hodgkin's lymphoma before and after histologic transformation. *Blood* 1989; 74:2579-2584.
 43. Vose JM, Kennedy BC, Bierman PJ, Kessinger A, and Armitage JO: Long-term sequelae of autologous bone marrow or peripheral stem cell transplantation for lymphoid malignancies. *Cancer (Phila.)*, 1992; 69:784-789.
 44. Darrington DL, Vose JM, Anderson JR, Bierman PJ, Bishop MR, Chan WC, Morris ME, Reed EC, Sanger WG, Tarantolo SR, Weisenburger DD, Kessinger A, and Armitage JO: Incidence and characterization of secondary myelodysplastic syndrome and acute myelogenous leukemia following high-dose chemoradiotherapy and autologous stem-cell transplantation for lymphoid malignancies. *J. Clin. Oncol.* 1994; 12:2527-2534.
 45. Stone RM, Neuberg D, Soiffer R, Takvorian T, Whelan M, Rabinowe SN, Aster JC, Leavitt P, Mauch P, Freedman AS, and Nadler LM: Myelodysplastic syndrome as a late complication following autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1994; 12:2535-2542.
 46. Marolleau JP, Brice P, and Gisselbrecht C: Secondary acute myeloid leukemia after autologous bone marrow transplantation for malignant lymphoma. *J. Clin. Oncol.* 1993; 11:590-591.
 47. Rohatiner A: Myelodysplasia and acute myelogenous leukemia after myeloablative therapy with autologous stem-cell transplantation. *J. Clin. Oncol.* 1994; 12:2521-2523.
 48. Miller JS, Arthur DC, Litz CE, Neglia JP, Miller WJ, and Weisdorf DJ: Myelodysplastic syndrome after autologous bone marrow transplantation an additional late complication of curative cancer therapy. *Blood* 1994; 83:3780-3786.
 49. Jones RJ, Ambinder RF, Piantadosi S, and Santos, GW: Evidence of a graft-versus-lymphoma effect associated with allogeneic bone marrow transplantation. *Blood* 1991; 77:649-653.
 50. Ratanatharathorn V, Uberti J, Karanes C, Abella E, Lum LG, Momin F, Cummings G, and Sensenbrenner LL: Prospective comparative trial of autologous versus allogeneic bone marrow transplantation in patients with non-Hodgkin's lymphoma. *Blood* 1994; 84:1050-1055.
 51. Chopra R, Goldstone AH, Pearce R, Philip T, Petersen F, Appelbaum F, DeVol E, and Ernst P: Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma. A case-controlled analysis of the European bone marrow transplant group registry data. *J. Clin. Oncol.* 1992; 10:1690-1695.
 52. Van Besien KW, Mehra RC, Giralt SA, Kantarjian HM, Pugh WC, Khouri IF, Moon Y, Williams P, Andersson BS, Przepiorka D, McCarthy PL, Gajewski JL, Deisseroth AB, Cabanillas FF, and Champlin R: Allogeneic bone marrow transplantation for poor-prognosis lymphoma. Response, toxicity, and survival depend on disease histology. *Am. J. Med.* 1996; 100:299-307.

53. Anderson JE, Litzow MR, Appelbaum FR, Schoch G, Fisher LD, Buckner CD, Petersen FB, Crawford SW, Press OW, Sanders JE, Bensinger WI, Martin PJ, Storb R, Sullivan KM, Hansen JA, and Thomas ED: Allogeneic, syngeneic, and autologous bone marrow transplantation Hodgkin's disease. The 21-year Seattle experience. *J. Clin. Oncol.* 1993; 11:2342-2350.
54. Gajewski JL, Phillips GL, Sobocinski KA, Armitage JO, Gale RP, Champlin RE, Herzig RH, Hurd DD, Jagannath S, Klein JP, Lazarus HM, McCarthy PL, Pavlovsky S, Petersen FB, Rowlings PA, Russell JA, Silver SM, Vose JM, Wiernik PH, Bortin MM, and Horowitz MM: Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease. *J. Clin. Oncol.* 1996; 14:572-578.
55. Milpied N, Fielding AK, Pearce RM, Ernst P, and Goldstone AH for the European Group for Blood and Marrow Transplantation. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. *J. Clin. Oncol.* 1996; 14:1291-1296.
56. Gulati SC, Shank B, Black P, Yopp J, Koziner B, Straus D, Filippa D, Kempin S, Castro-Malaspina H, Cunningham I, Berman E, Coleman M, Langleben A, Colvin OM, Fuks Z, O'Reilly R, and Blarkson B: Autologous bone marrow transplantation for patients with poor-prognosis lymphoma. *J. Clin. Oncol.* 1988; 6:1303-1313.
57. Baro J, Richard C, Calavia J, Gonzalez-San Miguel JD, Bello-Fernandez C, Alsar MJ, Gomez-Casares MT, Iriondo A, Conde E, Hermosa V, Garijo J, and Zubizarreta A: Autologous bone marrow transplantation as consolidation therapy for non-Hodgkin's lymphoma patients with poor prognostic features. *Bone Marrow Transplant.* 1991; 8:283-289.
58. 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, and 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* 1992; 80:1130-1134.
59. Freedman AS, Takvorian T, Neuberger D, Mauch P, Rabinowe SN, Anderson KC, Soiffer RJ, Spector N, Grossbard M, Robertson MJ, Blake K, Coral F, Canellos GP, Ritz J, and 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.* 1993; 11:931-936.
60. Jackson GH, Lennard AL, Taylor PR, Carey P, Angus B, Lucraft H, Evans RG, and Proctor SJ: Autologous bone marrow transplantation in poor-risk high-grade non-Hodgkin's lymphoma in first complete remission. *Br. J. Cancer* 1994; 70:501-505.
61. Sweetenham JW, Proctor SJ, Blaise D, Laurenzi A, Pearce R, Taghipour G, and Goldstone AH: High-dose therapy and autologous bone marrow transplantation in first complete remission for adult patients with high-grade non-Hodgkin's lymphoma. The EBMT experience. *Ann. Oncol.* 1994; 5 (Suppl. 2):S155-S159.
62. Pettengell R, Radford JA, Morgenstern GR, Scarffe JH, Harris M, Voll PJ, Deakin DP, Ryder D, Wilkinson PM, and Crowther D: Survival benefit from high-dose therapy with autologous blood progenitor-cell transplantation in poor-prognosis non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1996; 14:586-592.
63. Philip T, Hartmann O, Biron P, Cahn JY, Pein F, Bordignon P, Souillet G, Gartner M, Lasset C, and Chauvin F: High-dose therapy and autologous bone marrow transplantation in partial remission after first-line induction therapy for diffuse non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1988; 6:1118-1124.
64. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van Der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL, Coiffier B, Biron P, Mandelli F, and Chauvin F: Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N. Engl. J. Med.* 1995; 333:1540-1545.
65. Haioun C, Lepage E, Gisselbrecht C, Bastion Y, Coiffier B, Brice P, Bosley A, Dupriez B, Nouvel C, Tilly H, Lederlin P, Biron P, Briere J, Gaulard P, and Reyes F for the Groupe d'Etude des Lymphomes de l'Adulte. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. *J. Clin. Oncol.* 1997; 15:1131-1137.
66. Martelli M, Vignetti M, Zinzani PL, Gherlinzoni F, Meloni G, Fiacchini , De Sanctis V, Papa G, Martelli MF, Calabresi F, Tura S, and Mande F: High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin, and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line chemotherapy: a prospective randomized Italian multicenter study. *J. Clin. Oncol.* 1996; 14:534-542.
67. Verdonck LF, van Putten WLJ, Hagenbeek A, Schouten HC, Sonneveld P, Van Imhoff GW, Kluin-Nelemans H, Raemaekers JMM, Van Oers RHJ, Haak HL, Schots R, Dekker AW, DeGast GC, and Lowenberg B: Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. *N. Engl. J. Med.* 1995; 332:1045-1051.
68. Gianni AM, Bregni M, Siena S, Brambilla C, DeNicola M, Lombardi F, Grandola L, Tarella C, Pileri A, Stern A, Valagussa P, and Bonadonna G: 5-year update of the Milan Center Institute randomized trial of high-dose sequential (HDS) vs MACOP-B therapy for diffuse large-cell lymphomas. *Proc. Am. Soc. Clin. Oncol.* 1994; 13:1263.
69. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, Chopra R, Milligan D, and Hudson GV: Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomized trial. *Lancet* 1993; 341:1051-1054.
70. Carella AM, Carlier P, Congiu A, Occhini D, Nati S, Santini G, Pierluigi D, Giordana D, Bacigalupo A, and Damasio E: Autologous bone marrow transplantation as adjuvant treatment for high-risk Hodgkin's disease in first complete remission after MOPP/ABVD protocol. *Bone Marrow Transplant.* 1991; 8:99-103.
71. Rohatiner AZS, Johnson PWM, Price CGA, Arnott SJ, Amess JAL, Norton AJ, Dorey E, Adams K, Whelan JS, Matthews J, MacCallum PK, Oza AM, and Lister TA: Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for recurrent follicular lymphoma. *J. Clin. Oncol.* 1994; 12:1177-1184.
72. Press OW, Eary JF, Appelbaum FR, Martin PJ, Badger CC, Nelp WB, Glenn S, Butchko G, Fisher D, Porter B, Matthews DC, Fisher LD, and Bernstein ID: Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone

- marrow support. *N. Engl. J. Med* 1993; 329:1219-1224.
73. Bierman PJ, Vose JM, Leichner PK, Quadri SM, Armitage JO, Abrams RA, Klein J, Dicke KA, and Vriesendorp HM: Yttrium 90-labeled antiferritin followed by high-dose chemotherapy and autologous bone marrow transplantation for poor-prognosis Hodgkin's disease. *J. Clin. Oncol.* 1993; 11:698-703.
74. Soiffer RJ, Murray C, Cochran K, Cameron C, Wang E, Schow PW, Daley JF, and Ritz J: Clinical and immunologic effects of prolonged infusion of low-dose recombinant interleukin-2 after autologous and T-cell depleted allogeneic bone marrow transplantation. *Blood* 1992; 79:517-526.