Autologous Bone Marrow Transplantation for Aggressive Non-Hodgkin’s Lymphoma: Lessons Learned and Challenges Remaining

Richard I. Fisher

Long-term follow-up of numerous single-institution and national cooperative group clinical trials have confirmed that at least one third of all patients with advanced-stage, aggressive non-Hodgkin’s lymphoma (NHL) are cured by their initial treatment with combination chemotherapy. Results of the National Cancer Institute (Bethesda, MD)-sponsored High Priority Lymphoma Study established CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) as the standard therapy for these patients because it was equally as effective as any of the other popular regimens while being less toxic and less costly (1).

However, more than half of these patients were not being cured by available therapy. The next new treatment approach that improved the overall survival of patients with the advanced stages of aggressive lymphoma was the treatment of relapsed patients with high doses of chemotherapy with or without radiotherapy followed by necessary bone marrow reconstitution with autologous stem cells. This entire salvage treatment program will be referred to as AMBT (autologous bone marrow transplantation) throughout this editorial. Initially, bone marrow was the source of the stem cells; later peripheral blood stem cells largely replaced bone marrow. Fortunately, we have a prospective randomized trial that demonstrated the superiority of ABMT compared with standard salvage chemotherapy and established salvage ABMT as the standard therapy for all eligible patients with relapsed aggressive lymphoma (2). A similar conclusion had been reached by the GELA (Groupe d’Etude des Lymphomes de l’Adulte) LNH-87 (5) and the Italian Non-Hodgkin’s Lymphoma Cooperative Group (6). The EORTC trial had many of the problems seen in other ABMT randomized trials. Accrual was quite slow, and ultimately the trial was closed prematurely when it was calculated that additional patients were unlikely to change the final results. For a variety of medical and other reasons, only 60 of the 98 patients randomly assigned to receive ABMT actually received the transplant. These patient numbers were not sufficient to complete meaningful subset analyses.

Several attempts have been made to initiate ABMT earlier in the treatment program, i.e., before the standard chemotherapy had been completed. The Dutch HOVON (Dutch Organization for Hemato-Oncology in Adults) trial (7) and the subsequent GELA LNH-93 trial (8) actually demonstrated a benefit to completion of the conventional chemotherapy compared with early ABMT.

Affiliations of author: Cardinal Bernardin Cancer Center, Loyola University Stritch School of Medicine, Maywood, IL, and Lymphoma Committee, Southwest Oncology Group Operations Office, San Antonio, TX.

Correspondence to: Richard I. Fisher, M.D., Cardinal Bernardin Cancer Center, Loyola University Stritch School of Medicine, Rm. 255, 2160 S. First Ave., Loyola University Medical Center, Maywood, IL 60153.

© Oxford University Press
Thus, there seems to be no indication to add ABMT to the initial combination chemotherapy treatment for all patients with aggressive lymphoma. Fortunately, there is some hope that ABMT might be useful for selected subsets of these patients. Investigators from throughout the world collected data from more than 5000 cases of aggressive lymphoma treated with doxorubicin-based combination chemotherapy and were able to develop the International Prognostic Factor Index (IPI) that accurately assigns patients to low-, low-intermediate-, high-intermediate-, or high-risk groups defined by their expected failure-free and overall survival (9). There is no information from any of the previously mentioned studies to suggest that ABMT adds any benefit to the initial treatment of low-risk patients with aggressive NHL. However, when the IPI was retrospectively applied to the GELA LNH-87 study, a failure-free and overall survival benefit was demonstrated for the high-intermediate and high-risk groups (10). A retrospective subset analysis of the Italian trial yielded similar results (6).

These analyses were consistent with the hypothesis that high-intermediate- and high-risk young patients who responded to full-course CHOP chemotherapy would benefit from immediate stem-cell transplant compared with stem-cell transplant at relapse. To test this hypothesis, the leadership of the Lymphoma Committees of the Southwest Oncology Group, Eastern Cooperative Oncology Group, and Cancer and Acute Leukemia Group B have joined to initiate S9704, a prospective, randomized phase III comparison of early versus delayed high-dose therapy for patients with high-intermediate and high-risk diffuse large B-cell lymphoma. Patients will be randomly assigned to receive standard therapy (i.e., eight cycles of CHOP), followed by salvage ABMT if relapse occurs, or six cycles of CHOP followed by immediate ABMT. Patients eligible for this study would include any patient younger than 65 years of age who present with at least two or three of the following risk factors: advanced stage, i.e., stage III or IV; a lactate dehydrogenase level above normal; or a performance status of 2–4. These patients have a 5-year overall survival of only 32%–46% with current therapy. If successfully completed, this trial should define whether ABMT has a role in the initial treatment of poor-risk patients with aggressive NHL.

REFERENCES