Randomized trials are defining the role of autologous stem-cell transplantation in aggressive non-Hodgkin’s lymphoma (NHL), but there is less experience with this treatment in follicular lymphomas. Approximately 40% to 50% of patients with follicular NHL are in remission 4 to 5 years following autologous stem-cell transplantation. Results from phase II studies and retrospective analyses are remarkably similar, despite differences in patient populations, preparative regimens, use of purging, and source of stem cells. Nevertheless, there is little evidence of a plateau in disease-free survival curves, and we do not know whether patients are cured or overall survival is prolonged. Relapses 9 years following transplantation have been described.[1]

In their review, Freedman et al do not make recommendations about the timing of transplantation. Retrospective analyses show that results are better in patients with sensitive disease who have not been heavily pretreated. However, these patients are most likely to respond to any treatment modality. Decisions on timing have become more difficult since the introduction of rituximab (Rituxan), and likely will be further complicated when the iodine-131–labeled anti-CD20 antibody (tositumomab [Bexxar]) soon becomes available.

The authors also discuss the role of autologous transplantation in patients whose disease has undergone histologic transformation. They report that prolonged disease-free survival is possible for these patients but that no survival plateau has been achieved.[2] A European Bone Marrow Transplant Registry (EBMTR) analysis estimated the 5-year progression-free survival rate to be 33% for patients with transformed lymphoma.[3] Results were similar to patients without transformation, and the authors came to the same conclusion as do Freedman et al; namely, that autologous stem-cell transplantation is a reasonable approach, at least for patients with sensitive disease.

Transplantation During First Remission
The apparent lack of a plateau in disease-free survival following autologous transplantation for relapsed follicular NHL has led to trials of transplantation during first remission. Unfortunately, results from the Dana-Farber group and others have failed to document a survival plateau in these patients.[4,5] The group’s projected 3-year overall survival rate of 89% does offer the hope that autologous transplantation may prolong overall survival, however.

Investigators at Stanford performed autologous stem-cell transplantation in 37 patients with follicular NHL in first remission.[6] The actuarial 5-year overall survival rate was 87%. The outcome of these patients will be compared with historical controls before more transplants are performed. Caution is warranted because most trials of early transplantation have reported outcomes only for transplanted patients, and not for the entire denominator of all patients at the time of diagnosis. The long natural history of low-grade lymphoma makes it difficult to demonstrate overall survival advantages with any treatment. The authors discuss the use of surrogate end points, such as the absence of polymerase chain reaction (PCR)–detectable lymphoma cells in bone marrow following transplantation.

Role of Purging
The role of purging in autologous stem-cell transplantation for NHL is controversial. The authors review their own studies demonstrating that patients who receive contaminated autologous grafts are more likely to relapse than are patients who receive uncontaminated marrow.
A recent French analysis demonstrated that relapse was less likely in NHL patients whose marrow was purged more aggressively.[7] An EBMTR analysis showed improved overall survival (but no difference in progression-free survival) in low-grade NHL patients who received purged autografts.[8] These trials provide additional indirect evidence for the value of purging, although prospective trials are needed.

A European trial attempted to address this issue.[9] Patients with relapsed follicular lymphoma received three cycles of salvage chemotherapy. Responders were randomized to three more cycles of chemotherapy, unpurged autologous stem-cell transplantation, or purged autologous stem-cell transplantation. This trial closed early due to poor patient accrual.

A preliminary analysis showed that patients treated with chemotherapy have a significantly higher relapse rate than transplanted patients, although no differences between purged and unpurged transplants have been noted.[personal communication, H. Schouten, August 1999] In the absence of firm data, many believe that it is reasonable to attempt purging or transplantation with purified CD34+ progenitor cells as long as it is not associated with other toxicity.

**Allogeneic Transplantation**

Compared with autologous stem-cell transplantation, allogeneic transplantation has the potential advantages of uncontaminated marrow and a graft-vs-lymphoma effect. Freedman et al note lower relapse rates after allogeneic transplantation for NHL than after autologous grafting. These reports support the existence of a graft-vs-lymphoma effect. Further support comes from reports of lymphoma regression after withdrawal of immunosuppression in patients who relapse after allogeneic transplantation.[10]

The International Bone Marrow Transplant Registry results of allogeneic transplantation for low-grade lymphoma suggest the presence of a survival plateau.[11] However, nonrelapse mortality has been 30% to 40% in most series. A French registry analysis revealed an actuarial relapse rate of 12% at 5 years following allogeneic transplantation, as compared with a rate of 55% following autologous stem-cell transplantation (P < .001).[12] Event-free survival at 4 years was estimated to be 53% with allogeneic transplantation vs 45% with autologous transplantation. No events were observed later than 15 months after allogeneic transplantation, whereas a continuous pattern of progression was observed after autologous grafting. These results suggest that it may take several years before any survival advantage of allogeneic transplantation can be detected.

An EBMTR analysis also compared the results of autologous vs allogeneic transplantation for low-grade NHL.[13] Despite a higher relapse rate, overall survival at 4 years was significantly higher following autologous stem-cell transplantation, because of the high mortality associated with allogeneic transplantation.

The low relapse rate following allogeneic transplantation provides strong support for the use of immunotherapy for low-grade lymphoma. Freedman et al mention the use of low-intensity allogeneic transplantation. This approach may be able to exploit a graft-vs-lymphoma effect with lower mortality than does [conventional] allogeneic transplantation. There is intense interest and enthusiasm for low-intensity allogeneic transplantation.[14] However, a therapy rarely provides [something for nothing] and mature data are needed to sort out the benefits vs risks of this approach.

**Conclusions and Future Directions**

Despite the increasing use of transplantation in patients with follicular lymphoma, its role remains undefined. Ultimately, randomized trials may be the only way to determine whether the "emperor is wearing any clothes." Freedman et al discuss the use of various post-transplant treatments to improve results. Several ongoing trials are evaluating the use of rituximab either combined with or following autologous stem-cell transplantation for follicular NHL. The use of vaccination after autologous transplantation is also discussed; preliminary reports suggest that cellular and humoral immune responses can be generated soon after autologous stem-cell transplantation for lymphoma.[15]

**References:**


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