Review

High-dose chemotherapy and hematopoietic stem cell transplantation for relapsed or refractory diffuse large-cell non-Hodgkin's lymphoma

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Summary

The use of high-dose chemotherapy and transplantation for chemotherapy sensitive relapsed diffuse large-cell non-Hodgkin's lymphoma is now the gold standard for patients who are candidates for such therapy. Recent data also demonstrates the relative effectiveness of this approach for patients who are induction failures but are continuing to respond to conventional therapy at the time of transplantation. Newer approaches such as the use of novel agents to modify the transplant regimen, newer cytokines, or alternative sources of hematopoietic stem cells need to be tested in order to improve the outcome in patients with chemotherapy resistant disease.

Key words: autologous transplant, non-Hodgkin's lymphoma

The use of conventional dose anthracycline-containing chemotherapy for the treatment of advanced diffuse aggressive non-Hodgkin's lymphoma has now been well documented to produce long-term disease-free survival in 40%-45% of an unselected patient population [1-3]. High-dose chemotherapy and hematopoietic stem cell transplantation was first applied to the 55%-60% of patients either failing induction chemotherapy or relapsing at a later date. Initial clinical reports of transplantation in relapsed patients demonstrated that approximately 40% of patients with chemotherapy sensitive disease had long term disease-free survival compared with 10%-15% for chemotherapy resistant patients [4-8].

A concern of many single institution pilot studies has been that patient selection played an important part in the excellent outcomes of transplanted patients. In an attempt to decrease some of this bias, an analysis of 244 patients who underwent unsuccessful therapy or relapsed after receiving the LNH-84 protocol were evaluated to determine the result of any salvage therapy administered [9]. In this study, salvage treatment produced an objective response in 57% of the patients with a 23% second complete remission. The median overall survival was longer for patients who were treated with ABMT than for those who were treated with chemotherapy only (12.4 vs. 6.7 months), as was the median freedom from progression (FFP) survival (7.7 vs. 4 months). In a multivariate analysis, ABMT and normal initial lactic dehydrogenase (LDH) level were the primary parameters associated with longer survival.

Because of the concern of selection bias, a large international randomized trial (the Parma Study) was initiated to test conventional salvage therapy compared to high-dose chemotherapy and autologous hematopoietic stem cell transplantation for treatment of chemotherapy sensitive relapsed aggressive NHL [10]. A total of 215 patients with relapsed NHL were treated between 1987 and 1994 in this multicenter trial. All patients received two cycles of DHAP salvage chemotherapy (cisplatin, cytarabine, and dexamethasone) to test chemotherapy sensitivity. The 109 patients who had a response to chemotherapy were randomly assigned to receive four courses of chemotherapy plus involved field radiotherapy (54 patients) or involved field radiotherapy followed by intensive chemotherapy and autologous bone marrow transplantation (55 patients).

The overall rate of response to conventional chemotherapy was 58%. There were three deaths from toxic effects among the patients in the transplantation group, and none among those in the group receiving chemotherapy without transplantation. With a median follow-up time of 63 months, the overall response rate was 84% after autologous transplantation and 44% after chemotherapy without transplantation. At five years, the rate of event-free survival was 46% in the transplantation group and 12% in the group receiving chemotherapy without transplantation (P = 0.001, Figure 1), and the rate of overall survival was 53% and 32%, respectively (P = 0.038, Figure 2).

With the positive results of the Parma trial, the previously unconfirmed superiority of high-dose chemotherapy and hematopoietic stem cell transplantation over conventional salvage chemotherapy have now been validated. The procedure should be considered the standard of care for patients with chemotherapy sensitive relapsed aggressive NHL. The further improvement of transplantation for chemotherapy sensitive relapsed aggressive NHL will rely on the ability to improve transplantation...
regimens, improve the disease status of patients prior to transplant, or to use novel agents or immunomodulatory techniques to decrease minimal residual disease post transplant.

With respect to improving the disease status of patients prior to transplantation, a number of chemotherapy regimens have been tested. Regimens often utilized in relapsed patients include the DHAP regimen as used in the Parma trial [11], the MINE/ESHAP regimen (mesna, ifosfamide, mitoxantrone, etoposide, /etoposide, methylprednisone, high-dose cytarabine, cisplatin) [12], infusional regimens such as the CDE regimen (cyclophosphamide, doxorubicin and etoposide) [13], or mini-Beam (BCNU, etoposide, cytarabine, melphalan) [14]. Although no randomized trials have been performed, the current regimens all appear to produce approximately a 40%-50% chemotherapy sensitive response rate in relapsed patients. Perhaps further investigation of alternative combinations or novel agents can improve upon these results.

Improvements in the transplant regimen itself could also potentially improve the outcome for patients with relapsed aggressive NHL. Although many different regimens have been used in this clinical situation, no randomized trials have been performed. Some transplant centers feel that the use of total body irradiation (TBI) is essential and may translate into improved outcome for patients [15, 16]. However, other centers see an increase in acute and long-term toxicities with a TBI regimen including an increased incidence of secondary myelodysplasia and acute leukemias [17]. Only a prospective randomized trial would allow a thorough analysis of this question.

The other area of active investigation is the use of biologic response modifiers post-transplant or the use of antibody preparations during or post-transplant. Several pilot trials using interleukin-2 (IL-2) post-transplant in a minimal disease state have been reported [18–20]. The preliminary data was felt to be sufficiently promising to take the use of IL-2 post-transplant forward to a prospective randomized trial which is currently being performed in the Southwest Oncology Group (SWOG). Other trials of interferon-α or interferon-γ post-transplant have also been published in pilot format [21] and larger randomized trials are currently ongoing. Post-transplant use of lymphoma antibodies has also been reported in pilot trials [22]. The adjuvant use of Anti-B4-blocked ricin after autologous bone marrow transplantation has been tested in a prospective randomized trial; however, results are not yet available. Other possible antibodies for use with or following transplantation include the Anti-CD20 B-cell antibodies either unconjugated, such as the I DEC C2B8 antibody [23] or conjugated with a radioimmunoconjugate, such as the BI antibody [24]. Further testing of these agents will provide clinical information on their use in this patient population.

For patients with either primary refractory or relapsed lymphoma that is chemotheraphy resistant, the use of high-dose chemotherapy and hematopoietic stem cell transplantation remains somewhat controversial. A recent analysis by the American Bone Marrow Transplant Registry (ABMTR) evaluated 221 patients who never achieved a complete remission prior to undergoing high-dose chemotherapy and autologous transplant [25]. The probabilities of progression-free and overall survival at three years were 32% ± 6% and 40% ± 7%. The only prognostic variable found to be significant in a multivariate analysis was sensitivity to prior chemotherapy (P = 0.0002). Patients with resistant disease had a three-year probability of survival of only 19% ± 12% compared to 48% ± 13% for those with sensitive disease. Therefore, for patients with residual disease following induction therapy that is not refractory or progressive, high-dose chemotherapy and transplantation remains a viable option with satisfactory outcomes.

For patients with relapsed disease that is chemoresistant, most studies continue to demonstrate a 10%-20% failure-free survival post-transplant with few patients benefitting from this approach [4, 7, 8]. The most beneficial approach to these patients would appear to be earlier identification, perhaps using the International Prognostic Index [26] and transplantation before chemotherapy resistance is allowed to progress such as
when the patient is in first remission, or alternatively perhaps modulating agents that reverse chemotherapy resistance such as cyclosporine or other novel Multidrug Resistant (MDR) modulators currently under study. The use of anti-lymphoma antibodies such as the IDEC C2B8 or BI (Anti-CD20) may also sensitize the lymphoma to the effects of the chemotherapy regimen. Further investigation of all these approaches is warranted.

References


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