The best reports of conventional-dose salvage chemotherapy for HD have been noted in patients with long initial remissions. This observation was first reported by investigators from the National Cancer Institute (NCI) who retreated patients with MOPP after relapse from an MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)-induced first complete remission. A second complete remission was seen in 93% of patients with initial remissions of at least 12 months, compared with 29% of patients with initial remissions of shorter duration. Follow-up data from the NCI again showed a high complete response rate of 85% with conventional-dose salvage chemotherapy in patients with initial remissions longer than 1 year. Most patients received MOPP therapy initially, and again at the time of relapse. Overall survival in these patients was projected to be only 24%. This discrepancy was largely caused by deaths from treatment-related causes such as acute leukemia. Failure-free survival for these patients was not reported. Of interest is a previous publication from the Vancouver group that failed to confirm the efficacy of MOPP salvage in patients who relapse after long MOPP-induced first remission.

The best results of conventional-dose salvage chemotherapy for relapsed HD have been reported by the group from Milan. They reported a 51% freedom from progression after conventional-dose salvage chemotherapy in patients who relapsed after initial complete remissions of at least 1 year. Initial therapy in these patients was MOPP, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), or alternating MOPP/ABVD. Results of salvage chemotherapy were similar whether patients were retreated with the same regimen or received non-cross-resistant therapy. As was seen at the NCI, several patients in this series also died from second malignancies and cardiopulmonary complications of therapy. These patients were censored in the analysis of freedom from progression. A more recent abstract from Milan examined patients who relapsed after treatment with alternating MOPP/ABVD. Most received the same regimen as salvage. The freedom from progression was 46% for those patients with remissions longer than a year.

How should the results of the current study be interpreted in light of results achievable with conventional doses of salvage chemotherapy? The investigators report a 64% progression-free survival for the entire group of 58 patients. This is better than any results reported for conventional-dose salvage chemotherapy, regardless of initial remission duration.

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EDITORIAL

Autologous Transplantation for Hodgkin’s Disease: Coming of Age?

By Philip J. Bierman, Julie M. Vose, and James O. Armitage

It is now more than 10 years since the first reported use of high-dose chemotherapy with autologous bone marrow transplantation (ABMT) for patients with relapsed Hodgkin’s disease (HD). There has since been an explosion in the use of this form of therapy, and a large number of reports have appeared in the last year alone. The North American Autologous Bone Marrow Transplant Registry has recorded approximately 1,500 autotransplants for HD since 1989. It is likely that this represents only a fraction of the total number of transplants being performed.

Although results of transplantation for HD have generally been better than those seen after conventional-dose salvage therapy, the validity of transplant results has been questioned because of a lack of randomized trials and the possibility of selection bias. Early use of autologous transplantation for HD has often been delayed because of concerns about mortality, which has exceeded 20% in some series, and because of the high cost of transplantation. Furthermore, high complete response rates have been reported with conventional-dose salvage chemotherapy or radiation therapy for relapsed HD. The fundamental question is whether a clinical dose-response effect exists for HD that can be exploited with the use of autologous bone marrow rescue.

The report by Reece et al in this issue of BLOOD provides help in understanding the potential contribution of ABMT in managing patients with HD. The group from Vancouver has reported results of high-dose chemotherapy with ABMT in a group of HD patients who have relapsed from their first chemotherapy-induced complete remission. Previous reports of ABMT for HD have included patients with various amount of prior chemotherapy. Because first relapse is the most favorable clinical situation for any type of second-line therapy, this report provides a more direct way to compare transplantation results with the best reported results of conventional-dose salvage chemotherapy.

The best reports of conventional-dose salvage chemotherapy for HD have been noted in patients with long initial remissions. This observation was first reported by investigators from the National Cancer Institute (NCI) who retreated patients with MOPP after relapse from an MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)-induced first complete remission. A second complete remission was seen in 93% of patients with initial remissions of at least 12 months, compared with 29% of patients with initial remissions of shorter duration. Follow-up data from the NCI again showed a high complete response rate of 85% with conventional-dose salvage chemotherapy in patients with initial remissions longer than 1 year. Most patients received MOPP therapy initially, and again at the time of relapse. Overall survival in these patients was projected to be only 24%. This discrepancy was largely caused by deaths from treatment-related causes such as acute leukemia. Failure-free survival for these patients was not reported. Of interest is a previous publication from the Vancouver group that failed to confirm the efficacy of MOPP salvage in patients who relapse after long MOPP-induced first remission.

The best results of conventional-dose salvage chemotherapy for relapsed HD have been reported by the group from Milan. They reported a 51% freedom from progression after conventional-dose salvage chemotherapy in patients who relapsed after initial complete remissions of at least 1 year. Initial therapy in these patients was MOPP, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), or alternating MOPP/ABVD. Results of salvage chemotherapy were similar whether patients were retreated with the same regimen or received non-cross-resistant therapy. As was seen at the NCI, several patients in this series also died from second malignancies and cardiopulmonary complications of therapy. These patients were censored in the analysis of freedom from progression. A more recent abstract from Milan examined patients who relapsed after treatment with alternating MOPP/ABVD. Most received the same regimen as salvage. The freedom from progression was 46% for those patients with remissions longer than a year.

How should the results of the current study be interpreted in light of results achievable with conventional doses of salvage chemotherapy? The investigators report a 64% progression-free survival for the entire group of 58 patients. This is better than any results reported for conventional-dose salvage chemotherapy, regardless of initial remission duration.
Most of the patients received a brief course of conventional-dose salvage chemotherapy or involved-field radiation therapy to reduce tumor bulk before receiving the high-dose chemotherapy transplant preparative regimen. It might be argued that the pretransplant conventional therapy contributed to the overall outcome as much as the high-dose chemotherapy itself. This point is irrelevant. The pretransplant conventional therapy should be considered part of an integrated treatment process that contributed to the excellent outcome for patients in this series.

A more important question is whether the results of the current series are better than those achievable with conventional-dose salvage chemotherapy. Although the 85% progression-free survival in patients with long initial remissions is far superior to the Milan results, we can’t be sure that the two populations were comparable with respect to other important prognostic variables. The presence of extranodal disease at relapse and the presence of B symptoms at relapse were associated with lower remission rates after salvage chemotherapy in the Milan experience, not at the NCI, and were important in the Vancouver experience.

The current results might also be criticized on the basis of a prior publication from the Vancouver group. They examined the results of four different salvage strategies in patients in first relapse of HD after primary chemotherapy. The different salvage approaches included MOPP-based salvage chemotherapy, doxorubicin-based salvage therapy, extended-field radiation, or high-dose therapy with autologous transplantation. Freedom from second failure was similar after any of these salvage modalities. Outcome depended more on prognostic factors that were present at the time of relapse than on the type of salvage used. Although not stated, it is certain that many of the patients in the present series were also part of the prior analysis. The report in this issue does not prove that the good prognosis patients would not have done just as well with conventional salvage chemotherapy or radiation therapy.

In the Vancouver series more than 25% of patients who might have been eligible for transplantation in first relapse were not transplanted. Although the investigators state that this group did not contain patients with poor prognostic characteristics, the issue of selection bias cannot be ignored. More than one fourth of the patients were referred from other provinces in Canada. We are not told how this group was selected for referral. It must also be noted that median follow-up was only 2.3 years. While this is longer than the follow-up reported for many transplant series, it cannot compare to the 20-year follow-up reported from the NCI. A large number of patients in the present series are still at risk for late events such as relapse and leukemia. At our institution, we have observed relapses more than 6 years after autologous transplantation for HD.

These criticisms cannot be resolved without a prospective comparison. Nonetheless, we believe that the results reported by Reece et al represent an improvement over those obtainable with conventional salvage chemotherapy. Results from our institution are similar to those reported from Vancouver. Failure-free survival at 4 years was projected to be 43% in a group of 84 patients receiving transplants after relapse from their initial chemotherapy-induced complete remission and was 57% in patients with an initial remission of at least 1 year. Although our results are subject to the same criticisms as the current study, they provide additional support for the superiority of high-dose chemotherapy over conventional-dose salvage regimens.

Perhaps the most compelling evidence for the superiority of high-dose therapy in relapsed HD comes from a recent report from the British National Lymphoma Investigation. This is the first randomized comparison of high-dose chemotherapy with conventional-dose salvage chemotherapy in patients with relapsed and refractory HD. In this trial patients with relapsed or refractory Hodgkin’s disease were treated with a combination of carmustine, etoposide, cytarabine, and melphalan at a conventional-dose level (mini-BEAM) or a high-dose level (BEAM) that required autologous bone marrow rescue. The actuarial 3-year event-free survival was significantly better in patients who received high-dose chemotherapy (53% v 10%). This trial was closed early.

What about transplantation in patients who fail to achieve an initial remission or who have short initial complete remissions? HD patients who fail to enter complete remission have a very poor prognosis. Such patients had a 0% projected failure-free survival in the Milan experience and a median survival of 16 months at the NCI. It is now believed that transplantation is the preferred option in this situation. Results from several series demonstrate that some of these patients may achieve prolonged disease-free survival after high-dose therapy and autologous transplantation. We have observed a 22% 3-year progression-free survival in 44 such patients. We believe these results provide strong evidence for the superiority of high-dose chemotherapy regimens in this setting.

What is the best approach for patients who have initial remissions of less than 12 months? In the Milan experience these patients had a failure-free survival of approximately 20%. Overall survival for patients with short initial remissions was only 11% at the NCI. Results from other series suggest that no more than 10% to 20% of such patients can expect long-term disease-free survival. In the current series, progression-free survival was 48% for patients with short initial remissions. This outcome is better than reports from any other salvage chemotherapy and lend support to the decision analysis reported by Desch et al that suggested that patients relapsing after a seven- or eight-drug regimen should receive transplants immediately, rather than receive conventional-dose salvage therapy. This analysis also suggested that patients with initial MOPP-induced remissions of less than 1 year should receive conventional salvage chemotherapy before attempting transplantation. However, there is no evidence that patients relapsing after a seven- or eight-drug regimen are more resistant to salvage therapy than those treated with a four-drug combination. There seems to be a strong argument for transplant after early relapse.

Despite better response rates with high-dose therapy, it can still be argued that the best strategy for patients with relapsed HD is the use of conventional salvage chemother-
apy first, and to save transplantation until second chemotherapy failure. This approach would eliminate the need for transplantation in the patients who would be cured with conventional-dose salvage chemotherapy. This argument may not be resolved without future trials that define the best and worst times for transplantation. However, the facts on which this argument is based may no longer be valid. Transplant-related mortality for HD in experienced centers is quite low. Mortality was only 5% in the present report and only 4% among first-relapse patients who received transplants at our institution.14 Reece et al note that these values are similar to the mortality seen in some reports of conventional-dose salvage chemotherapy. Our experience in Nebraska is similar to the Vancouver experience in which complication rates decreased as institutional experience with transplantation matured. In HD patients transplanted with cyclophosphamide, carmustine, and etoposide, we have not had any early-in-hospital mortality since September 1989 (approximately 140 transplants). The length of hospitalization has been dramatically shortened with the routine use of hematopoietic growth factors after transplantation. Patients are now routinely discharged within the first week after transplant and several centers are beginning to perform transplants on an outpatient basis. The toxicity and expense of transplantation may now be comparable with conventional therapy that must be administered over several months.

We feel that results of high-dose therapy followed by autologous transplantation are superior to those of conventional-dose salvage therapy in virtually all clinical situations. Autologous transplants for HD have become easier, less expensive and safer. We recommend transplant to patients after relapse from any front-line HD chemotherapy regimen, regardless of the length of initial remission. The results of the current study by Reece et al support this approach.

REFERENCES


Autologous transplantation for Hodgkin's disease: coming of age? [editorial; comment]

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