Development of Effective Salvage Treatment Programs for Hodgkin’s Disease: An Ongoing Clinical Challenge

By Richard T. Hoppe

The evolution of management programs for Hodgkin’s disease in the past three decades has served as a model for the development of effective cancer treatment programs. With contemporary management, only 20% to 30% of patients with Hodgkin’s disease will fail to achieve a complete response or relapse after the completion of primary therapy. Only one-half of those patients will achieve a durable complete response to secondary treatment and the remainder will eventually die from disease or the effects of continuous therapy. Prognostic factors at the time of relapse may include patient age and performance status, degree and duration of response after initial therapy, extent and sites of disease at relapse, and the type of salvage therapy.

The type of initial treatment plays an important role in the selection of suitable salvage therapy. For patients managed initially with irradiation alone the decision is usually simple. If an initial curative irradiation program for Hodgkin’s disease has failed, its value as a sole salvage therapy is limited. Quite effective systemic management programs are available for these patients. Chemotherapy or combined modality programs using MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone), MVPP (nitrogen mustard, vincristine, procarbazine, and prednisone), or ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) achieve a 5-year freedom from second progression of 60% to 80%. The value of adjuvant involved field irradiation in these patients is uncertain, supported by one study but not in another, when used selectively. However, because many of these patients experience a localized relapse, outside of previously irradiated fields, the addition of adjuvant irradiation may be accompanied by little attendant morbidity and it may increase the likelihood of local control. Areas of relapse within previously treated regions may be treated as well, albeit with lower doses.

A more challenging problem is the management of relapse in patients treated initially with chemotherapy. These patients may have resistant disease, which has failed to respond completely to (or even progressed during) initial treatment, or they may have achieved an initial complete clinical response and only later relapsed. Some of these patients, perhaps as many as 15% to 20%, may have a limited extent of relapse (ie, lymph nodes only, one side of the diaphragm) and may be candidates for salvage therapy with wide-field irradiation, such as subtotal or total lymphoid irradiation. In well-selected patients of this type, especially those without B symptoms and who have a long (>1 year) initial disease-free interval, this program may achieve long-term disease-free survival in 35% to 40%. Several reports support this approach, but the number of patients included in each is quite small.

More commonly, patients who relapse after initial treatment with chemotherapy are considered suitable candidates for systemic salvage programs. These programs may include retreatment with the same drugs, the use of non-cross-resistant chemotherapy programs, or investigational programs such as high-dose chemotherapy with autologous bone marrow rescue.

When patients achieve a complete response to MOPP but later relapse, retreatment with MOPP can achieve a complete response rate in 59%. In patients with a long duration of initial response (>12 months), the complete response rate to reinduction therapy is quiet high (93%). However, even in this very favorable group, the remissions achieved are not as durable as with primary therapy, and the majority experience a second relapse within 2 years.

The more usual choice of salvage therapy after primary MOPP failure is a non-cross-resistant regimen such as ABVD. ABVD offers a prospect for complete response not only to patients who responded initially to MOPP but also to those who had only partial responses or experienced disease progression while being treated with MOPP. Nevertheless, the likelihood of a complete response to salvage ABVD (52% to 80%) is still very dependent on the degree and duration of initial response to MOPP. Again, even for patients who achieve a complete response, the median duration of response is less than 2 years.

The prospects for effective salvage treatment with standard chemotherapy programs after failure of both MOPP and ABVD (either sequentially or combined) are poor. Only one-third or fewer patients will achieve a complete response to reinduction therapy with these programs.

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response to “third-line” chemotherapy programs such as CEP (CCNU [lomustine], etoposide, and prednimustine) or MIME (Methyl-GAG, ifosfamide, methotrexate, and etoposide). It is not clear that the long-term outcome of management with these agents is any better than might be expected from the judicious use of palliative single-agent chemotherapy.

The inability of further chemotherapy to achieve long-term disease-free survival after primary chemotherapy failure in the majority of patients, combined with the well-established dose intensity-disease control relationships demonstrated for Hodgkin’s disease, has led to the introduction of high-dose chemotherapy-autologous bone marrow rescue programs in this setting. A growing number of studies now report significant numbers of patients managed in this fashion. The precise high-dose preparatory regimens (including choice of drugs, drug doses, timing of administration, and use of radiation therapy), use of prior cytoreductive therapy, and selection of patients varies substantially. Patients analyzed in these trials often include some with resistant disease after single or multiple treatment programs, some who have relapsed after complete responses, and even some who have been successfully cytoreduced before high-dose therapy. As with any new modality, the initial patients studied were in the most unfavorable clinical situations and there was an attendant poor outcome and excessive rate of fatal toxicity (as high as 26%). As more favorable patients have been accrued to studies, the results (response rates and durability of responses) have improved and fatal toxicity has now been reduced to an average of only about 10%.

However, given the heterogeneity of patients in each of these series, the precise role of autologous bone marrow transplantation (ABMT), in contrast to traditional salvage therapies, has not been defined. In the current issue of Blood, Lohri et al, from the Cancer Control Agency of British Columbia, address this question. They review their institutional experience with different salvage treatment programs among patients who have relapsed after achieving a complete response to primary therapy. Primary treatment programs included MOPP, MOPP with irradiation, and MOPP/ABV (or MOPP/ABV hybrid). Salvage treatment programs included wide-field irradiation, reinduction with MOPP, treatment with doxorubicin-containing chemotherapy, and cytoreduction with MVPP or involved field irradiation followed by high-dose chemotherapy (cyclophosphamide, BCNU, and etoposide) and ABMT. They report that the success of the salvage treatment programs was more dependent on patient characteristics at presentation and relapse than on the particular salvage program used. Specifically, patients who had either stage IV disease at presentation, B symptoms at relapse, or a disease-free interval less than 1 year had a poor outcome, even with ABMT, whereas patients with no unfavorable characteristics had a good outcome with any of the well-defined salvage programs.

These results are somewhat surprising, and there are possible explanations. As in all other series of ABMT salvage, the number of patients in each category that have similar clinical characteristics is small. Simply “bad luck” (or subtle factors of poor selection) in a treatment group with very few patients may leave a negative impression regarding the outcome of treatment. In this report, ABMT after MOPP/ABV(D) in a group of 12 “unfavorable” patients yielded a 3-year freedom from second failure of only 19%. In contrast, in a report published recently from the Milan Cancer Institute, nine patients who had an initial complete response to MOPP/ABV(D) had a 3-year freedom from second progression of 76% after ABMT salvage. According to the published data, these patients appear to have similar characteristics, but much different outcomes. This result may be due to differences in ABMT treatment regimens, but is more likely a problem of small numbers. Neither series includes enough patients to provide a definitive answer.

Despite the problem of small numbers, this report does raise important questions regarding salvage therapy in Hodgkin’s disease. It is unique in its effort to compare the outcome of ABMT with that of traditional salvage programs among patients treated at a single institution, stratified by the same prognostic factors. All patients were included who were treated during a defined period of time, who achieved a complete response to primary chemotherapy, and who later relapsed. Patient characteristics at presentation and relapse were carefully matched to define favorable and unfavorable groups. Short of a prospective randomized trial, which may never prove feasible, this type of careful analysis may hold the best potential for identifying the role of ABMT in Hodgkin’s disease. Other large institutions with significant experience in the primary and salvage treatment of Hodgkin’s disease should undertake similar analyses to identify prognostic factors and compare the outcome of different salvage treatment programs. With thoughtful studies of this type, the precise role for ABMT in the curative management of Hodgkin’s disease will eventually be defined.

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