Hodgkin's Disease: Management of First Relapse

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In most patients with newly diagnosed Hodgkin's disease, initial therapy is curative. However, a small portion of patients treated with radiotherapy alone for limited favorable disease, and a larger percentage of patients treated with combination chemotherapy, with or without radiotherapy, for advanced-stage or unfavorable disease relapse after initial remission. Patients relapsing after radiotherapy alone should do as well with salvage combination chemotherapy as patients with advanced disease who have never received radiation. In patients who relapse after combination chemotherapy, retreatment with the same regimen or employment of a non-cross-resistant regimen offers high response rates among those with favorable characteristics.

Introduction

The vast majority of patients diagnosed with Hodgkin's disease are cured with initial treatment. However, a small number of patients treated with radiotherapy alone for limited disease, and a larger percentage of patients treated with combination chemotherapy, with or without radiotherapy, for advanced-stage or unfavorable disease relapse after attaining an initial remission. This review will focus on the management of patients at first relapse from an initial complete remission. Patients in whom induction therapy fails will not be discussed per se, although some data pertaining to this group will be presented because of the heterogeneity of patient populations in studies of second-line treatments.

The review is divided according to the general situations that arise in the treatment of patients at first relapse. These include relapse after initial radiotherapy alone and relapse after combination chemotherapy alone or combined with radiotherapy. The latter discussion is further divided according to the following treatment modalities: conventional chemotherapy, radiotherapy, and high-dose therapy with autografting.

Relapse After Primary Radiotherapy

Primary radiotherapy is an effective treatment for selected patients with favorable early-stage Hodgkin's disease, staged either clinically or surgically. Treatment with extended-field radiation offers high response rates and long remissions in most patients. Nonetheless, 20% to 30% of patients relapse within 5 years after initial radiotherapy [1,2].

Combination Chemotherapy

A considerable body of evidence shows that patients who relapse after primary radiotherapy can be treated effectively with combination chemotherapy. Table 1 summarizes results from several large series in which MOPP (mechlorethamine, Oncovin, prednisone, and procarbazine) or a MOPP-based regimen was employed [3-10]. Complete response rates ranged from 72% to 95%, and most patients (50% to 80%) were alive and free of disease at 5 years following chemotherapy. Predictors of improved outcome were similar to those for patients treated de novo; these included small tumor burden and younger age at relapse [3-6,11]. In addition, Cadman et al found that a long duration of remission (> 12 months) was predictive of improved survival after relapse [6], although this observation was not confirmed by others [3,7].

Impact of Chemotherapy Regimen--The importance of the particular chemotherapy regimen employed at relapse following primary radiotherapy has been addressed in a number of trials. The Cancer and Leukemia Group B (CALGB) found higher complete response rates and longer durations of remission among patients who received a lomustine (CCNU [CeeNU])-containing regimen (CVPP [CCNU, vinblastine, procarbazine, and prednisone] or COPP [CCNU, Oncovin, procarbazine, and prednisone]) than in those given regimens that contained mechlorethamine (MOPP or MVPP [mechlorethamine, vinblastine, procarbazine, and prednisone]) [5]. Santoro et al [8] reported a clear benefit on complete response rate, failure-free survival, and overall survival with the use of a doxorubicin-containing regimen, compared to MOPP chemotherapy.
However, the advantage of doxorubicin was not confirmed in a CALGB study that compared CVPP to ABOS (Adriamycin, bleomycin, Oncovin, streptozotocin) to alternating CVPP/ABOS [4]. Although these studies showed the superiority of one regimen or agent over another, it is not clear whether the prior history of radiotherapy would necessarily influence the choice of chemotherapy at relapse.

**Primary Radiotherapy vs Initial Chemotherapy**--A number of authors have tried to determine whether patients who receive primary radiotherapy have a different prognosis at relapse than do patients presenting with advanced-stage Hodgkin's disease who have never received radiation. Several authors have reported higher complete response rates [5,9,10] and longer disease-free and overall survival [5] among patients who failed initial radiotherapy, compared to concurrent patients with advanced Hodgkin's disease treated with chemotherapy de novo. The better results could be explained by the more favorable characteristics of the group that received prior radiotherapy (fewer stage IV patients) [6,10].

One author [5] found that a history of prior radiotherapy was independently predictive of response and duration of response in multivariate analysis. However, the independent prognostic significance of this variable was not confirmed by others [9]. It appears that patients who relapse after primary radiotherapy have at least as favorable prognosis as patients with advanced-stage disease who did not receive radiotherapy.

In summary, the outcome of patients who relapse following initial treatment with radiotherapy alone is as favorable as, and possibly better than, patients requiring initial chemotherapy. The treatment program at relapse should be based on the efficacy and toxicity profile of a particular regimen, with consideration for the cumulative effects of prior radiation.

**Relapse After Primary Chemotherapy**

Combination chemotherapy, with or without radiotherapy, leads to a complete remission in the majority of patients with advanced-stage or unfavorable Hodgkin's disease. However, a significant fraction of these patients fail to experience long-term remissions. Over the last several decades, the management of patients at first relapse has changed with the introduction of new drugs, development of new ways of delivering chemotherapy, and better understanding of the prognostic factors at first relapse.

**Second-Line Chemotherapy**

**Retreatment with MOPP**--Fisher et al reported in 1979 that patients who initially achieved a complete response with MOPP chemotherapy could be successfully retreated with MOPP at first relapse [12]. In their study, 60% (19/32) of patients achieved a complete response (median duration, 21 months). Patients with an initial remission duration more than 12 months did particularly well; 93% (14/15) of these patients attained a complete response to a second course of MOPP, as compared with only 29% (5/17) of those with an initial remission duration less than 12 months. This observation was particularly interesting because it suggested that patients who relapsed after a complete response were not necessarily resistant to chemotherapy, and because it showed that a subset of patients could achieve a relatively durable remission after relapse.

A recent update of the first NCI series [13] includes patients treated at relapse with MOPP alone, MOPP with maintenance MOPP, or MOPP with radiotherapy. In total, 65% (35/54) patients achieved a second complete remission. Among those with an initial remission duration more than 12 months, 85% (28/33) achieved a second complete response. The actuarial disease-free survival for this group was estimated at a remarkable 45% at 20 years; however, only 24% were alive at 20 years due to secondary leukemia and other treatment-related complications.

The experience with primary MOPP and secondary MOPP treatment illustrates several important points that are echoed in the results of later second-line treatments:

1. The effectiveness of salvage chemotherapy depends, in great part, on the parameters of disease sensitivity, such as duration of remission.
2. Retreatment with the initial regimen can result in significant disease-free survival among selected patients.
3. Treatment-related toxicities may limit long-term survival, although these effects may not become apparent for several years, and possibly decades.

**Doxorubicin-Based Treatment After MOPP Failure**--The doxorubicin-based ABVD regimen (Adriamycin, bleomycin, vinblastine, and dacarbazine) was developed in 1973 by Bonadonna and colleagues specifically to treat MOPP-resistant patients. The combination includes drugs individually
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Effective in Hodgkin's disease but non-cross-resistant to MOPP components.
In 1991 Bonadonna et al presented updated results of the use of ABVD in 56 MOPP-resistant patients (induction failure or relapse within 12 months after a complete response) [14]. Of these, 22 patients (46%) achieved a second complete response, and the median survival was 28 months. Half of the patients who achieved a second complete response were still alive at 5 years. The second complete response rate was 65% for patients who achieved an initial complete response vs 33% for patients who failed induction therapy. The ABVD regimen clearly has activity in patients failing MOPP chemotherapy, and the results support the rationale for non-cross-resistant chemotherapy salvage regimens.

The very favorable results achieved by the Milan group with the ABVD regimen were not uniformly confirmed. Harker et al [15] described the results of treatment of 110 patients with advanced Hodgkin's disease who progressed on, or relapsed after, MOPP chemotherapy. Patients received either ABVD or B-CAVe (bleomycin, CCNU, Adriamycin, and vinblastine) in concurrent, but nonrandomized, trials. Only 38% of patients achieved a complete response to ABVD, and 44%, to B-CAVe. The 5-year actuarial freedom from progression was 8.5% for ABVD-treated patients vs 25% for B-CAVe-treated patients. The freedom from progression at 4 years was 45% and 55% among the complete responders to ABVD and B-CAVe, respectively.

These results are markedly less optimistic than those reported by the Milan group. However, many of these patients had been retreated with MOPP and/or radiotherapy, so that ABVD or B-CAVe did not necessarily represent true second-line treatment.

The effectiveness of ABVD and B-CAVe in the series by Harker et al depended, to a significant extent, on the durability of the initial response to MOPP. Among the 32 patients treated with ABVD for relapse after a complete response to MOPP chemotherapy, a second complete response was attained in 64% of the patients who relapsed after 12 months, as compared with 28% of the those who relapsed within 12 months. Similarly, among the 35 patients treated with B-CAVe after relapse from a complete response to MOPP, 61% of patients with a long remission achieved a second complete response, as opposed to 42% of those with a short duration of remission.

Tannir et al [16] tested a doxorubicin-based regimen called ABDIC (Adriamycin, bleomycin, dacarbazine, CCNU, and prednisone) in MOPP-resistant patients (induction failure or remission duration less than 12 months). The overall complete response rate was only 35%, but six of seven patients who had initially achieved a complete response with MOPP achieved a second complete response to ABDIC. About half of all patients who achieved a complete response were still free of disease at 3 years.

The CALGB conducted a randomized trial of MOPP, ABVD, and alternating MOPP-ABVD that showed a superiority of ABVD-based regimens over MOPP alone in the initial treatment of advanced-stage Hodgkin's disease [17]. Patients who failed MOPP or ABVD (induction failure, partial response to initial treatment, or relapse after complete response) were crossed over to receive the other regimen. Thus, 48 patients received ABVD as second-line treatment after failing MOPP. Only 35% (17/48) of these patients achieved a second complete response. The median failure-free duration of survival was 9 months, and the actuarial failure-free survival rate was only 20% at 4 years. However, more than two-thirds of patients treated secondarily with ABVD had failed, or obtained only a partial response to, initial MOPP therapy; data were not reported on the subgroup who relapsed after attaining a complete response.

As the results from Milan emphasized, patients who fail induction therapy have a considerably less favorable outcome than those who obtain an initial complete response. Thus, the overall group of MOPP failures in the CALGB study had particularly poor prognostic factors; estimation of the effectiveness of ABVD in this population is difficult because of its heterogeneity.

The results of doxorubicin-based salvage treatments in patients who fail to respond to MOPP clearly show activity of a non-cross-resistant regimen. The effectiveness of salvage treatment depends, in large part, on the extent and durability of the initial remission. Among patients who relapse after achieving an initial complete remission, roughly half may be expected to enter a second remission. However, only half of this subgroup is likely to still be in remission at 4 to 5 years. Thus, only a minority of patients would be expected to experience a sustained remission after relapsing from initial therapy.

**Second-Line Therapy After ABVD-Based Initial Therapy**—The activity of ABVD, first as a salvage regimen and later as initial therapy, alone or alternating with MOPP, has led to increasing numbers of patients whose primary therapy included ABVD. Few studies have evaluated the efficacy of second-line treatment for this contemporary group of patients. Particular concern has been raised about the efficacy of salvage following relapse with eight-drug regimens, in which the most active...
agents for Hodgkin's disease are used up front. In the CALGB trial comparing MOPP, ABVD, and MOPP-ABVD, 33 patients who failed ABVD were crossed over to receive MOPP salvage therapy [17]. Of these patients, 61% achieved a second complete remission. The 3-year failure-free survival of 40% in this group was considerably greater than that in patients who received ABVD as salvage after failure of MOPP (40% vs 20%). These favorable results of MOPP salvage after ABVD are in contrast to those reported by Bonadonna et al; in their study, only 25% (16/63) of patients who failed ABVD achieved a complete remission with MOPP therapy (median duration of remission, 16 months) [14]. However, details of the patient characteristics were not provided, and may account for the difference in outcome. Viviani et al [18] from Milan reported on 49 patients who had an initial remission longer than 12 months following initial treatment with MOPP (26 patients), ABVD (8 patients), or MOPP-ABVD (15 patients). Of these 49 patients, 44 received an ABVD-based salvage regimen, and 84% (41/49) achieved a complete response. There was no difference in attainment of a complete response among patients who were retreated with the same regimen, a non-cross-resistant regimen, or an alternating regimen that included the original regimen plus a non-cross-resistant component. Overall 5-year results were excellent, with a freedom from progression of 51% and an overall survival of 65%. The effectiveness of second-line therapies after initial ABVD, or an initial eight-drug regimen, can be surmised from retrospective reviews of patients treated at two large centers. A review of the NCI experience by Longo et al of 107 patients revealed no significant difference in outcome after first relapse between patients initially treated with MOPP and those treated with an initial eight-drug regimen [13]. Similarly, a review by Lohri et al of the Vancouver experience did not show any prognostic importance of the initial treatment regimen, whether it was MOPP, ABVD, or an eight-drug regimen [19]. However, both studies had a limited number of patients from whom conclusions could be drawn.

A number of etoposide (VePesid)-based salvage regimens following ABVD or eight-drug initial therapy have met with varying success. Santoro et al [20] described the results of treatment with with CEP (CCNU, etoposide, and prednimustine) in 58 patients who had failed both MOPP and ABVD, 28 of whom had failed MOPP. The CEP regimen was associated with 40% of these patients achieving a complete response (median duration, more than 15 months). Among patients with resistant disease (induction failure or relapse within 12 months), the complete response rate was 30%, compared with a complete response rate of 82% in patients with a long duration of remission. It is difficult to discern from this study whether the CEP regimen is superior to retreatment with the initial regimen among patients with a long duration of remission, although it is clear that the complete response rate in patients with resistant disease treated with CEP is poor. Pfreundschuh et al [21] reported on the use of CEVD (CCNU, etoposide, vindesine, and dexamethasone) in 32 patients resistant to COPP-ABVD, 27 of whom were were primarily resistant and 5 of whom had relapsed within 12 months of attaining a complete response. Overall, 44% of the patients achieved a second complete response to CEVD, with four of five patients in early relapse achieving a complete response (median duration of complete response, more than 10 months; median overall survival, more than 26 months).

Pfreundschuh et al [22] recently published a study describing the results of using Dexa-BEAM (dexamethasone, BCNU, etoposide, Ara-C, and melphalan) to treat 55 patients who progressed on or relapsed after 8- or 10-drug chemotherapy (COPP plus ABVD, or COPP plus ABV plus ifosfamide [Ifex], methotrexate, and etoposide). Overall, only 31% of patients achieved a complete response, with a 25% complete response rate among patients with progressive disease or an early relapse and a 60% complete response rate among those with a long duration of remission. In summary, the results of second-line treatment after initial therapy with ABVD or an eight-drug containing regimen show that the extent and duration of initial remission are important prognostic variables at relapse. Only a small minority of patients who fail to respond to induction therapy or relapse within 12 months achieve a second complete response. Patients with more favorable characteristics have a much higher likelihood of attaining a second remission either when retreated with the induction regimen or given a non-cross-resistant combination. However, even in this favorable group, a minority of patients are likely to be in remission at 4 years after relapse.

Second-line regimens containing etoposide have some activity, although it is unclear whether these regimens offer a significant advantage.

**Prognostic Variables at Relapse**—A recurrent theme throughout the studies discussed thus far is the prognostic importance of the extent and durability of the initial remission, irrespective of the specific initial or second-line treatment used. Patients with a long duration of initial remission fare better, regardless of whether their second-line treatment is retreatment with MOPP,
non-cross-resistant ABVD, or retreatment with ABVD. **Table 2** summarizes the results of salvage treatment according to the length of first complete remission [13-15,18]. Lohri and colleagues performed an extensive and formal analysis of predictive variables among 80 patients at first relapse [19]. They found that a relapse time of less than 1 year, stage IV disease at initial diagnosis, and B symptoms at relapse were predictive of outcome after relapse, irrespective of the type of salvage therapy. Patients with one or more of these factors had a rate of freedom from second failure of 17% at 5 years, as compared with a rate of 82% if none of the factors was present.

In the analysis of the NCI experience by Longo et al, among 109 patients at first relapse, age at diagnosis and length of remission were the only predictors of survival [13]. A long duration of remission predicted a higher complete response rate, more durable second remission, and longer overall survival.

Establishing important prognostic factors at relapse serves several useful purposes. One can identify groups of patients who would not expect to do well with current treatments, for whom future efforts can be directed. Also, one can pinpoint important variables that should be considered when evaluating the results of different, and particularly novel, treatment regimens.

**Salvage With Radiotherapy**

Several authors have reported on the results of using radiotherapy alone with curative intent following relapse after chemotherapy. These patients tend to be highly selected, having either disease limited to nodal areas or localized sites of extranodal involvement. **Table 3** shows the results of several larger retrospective analyses of salvage radiotherapy [11,19,23,24]. Most investigators used extended (subtotal or total nodal) radiation fields, although several used more limited regional (ie, mantle) radiation. All studies reported very high complete response rates, varying from about 90% to 100%. Rates of failure-free survival, however, ranged from 40% to 50% at 3 years following treatment.

**Predictors of Improved Outcome**--The parameters that were predictive of improved outcome following treatment with radiotherapy were similar to those that predict outcome after other forms of therapy. These factors include a long remission prior to relapse [11,13]. Longo et al [13] found that all four patients with localized relapse > 12 months following initial MOPP chemotherapy achieved a complete response to regional radiotherapy, and only one of them subsequently relapsed. In contrast, six patients with a duration of remission less than 12 months achieved a complete response, and five of the six relapsed.

Fox et al [23] reported an overall disease-free survival of 36% at 3 years among 17 patients treated with regional or extended radiotherapy. However, three of four patients with a remission duration more than 12 months were still in extended remission at the time of the report.

Other parameters that are predictive of improved outcome include disease limited to nodal sites of involvement at relapse [11] and younger age [23]. Lohri et al [19] analyzed the outcome of patients at first relapse, and found that three factors were highly predictive of outcome irrespective of the kind of salvage treatment: initial stage IV disease, B symptoms at relapse, and remission less than 12 months. Among the 17 patients in their series treated with total nodal radiation, the presence or absence of these three factors was highly predictive of outcome. Only 17% of those with all three poor prognostic factors had not suffered a treatment failure at 5 years follow-up, as compared with 100% of the six patients who lacked all three.

In summary, these studies show that radiotherapy can be used in selected patients to attain relatively long remissions. The factors predictive of favorable outcome are similar to those which would predict success with other modalities, such as combination chemotherapy. Since all of these studies are retrospective, however, it is unclear how these patients would have fared with other modalities.

**High-Dose Therapy and Autografting**

**Efficacy of Therapy**--High-dose therapy with autografting of either bone marrow or stem cells has been used with increasing frequency over the last 10 years in patients with refractory or relapsed Hodgkin's disease. As summarized in **Table 4**, recent studies generally report improved results, compared to historical conventional salvage strategies [22,25-30]. However, although overall results appear to be improved, there is still considerable variation between centers with regard to treatment-related mortality and outcome, as measured by either event-free survival, freedom from progression, or overall survival.

It is difficult to compare the results from different centers since the studies may vary in the preparative regimen administered, the type of autograft utilized, and the distribution of prognostic factors among study patients. Moreover, it may even be difficult to compare results obtained at the
same center over time. For example, the series from Anderson et al [29] in Seattle represents over two decades of work, during which time the transplant procedure and patient selection were still very much in evolution.

The patient characteristics that are predictive of favorable outcome with high-dose therapy are similar to those that predict outcome in de novo patients. Important factors include fewer relapses [28-30], nodal disease only, absence of B symptoms at relapse [27], less disease at transplantation [25,30], sensitive disease at transplantation [28,30], and better performance status [30]. Because of the number of prognostic factors and general heterogeneity of patient populations, studies that focus on a particular group of patients or particular treatment strategy are especially important. Two groups have reported on the results of high-dose therapy in patients at first relapse. Reece and colleagues [27] treated 58 patients in first relapse after combination chemotherapy. Treatment-related mortality was 6.6%. At 4 years, 64% of the entire group had not progressed, while over 80% of the 23 patients with an initial remission more than 1 year were progression-free. Median follow-up was 2.3 years.

Bierman and colleagues [31] treated 84 patients in first relapse. Most (63%) achieved a complete response, and only 4% died from treatment-related causes. At 4 years, 43% were failure-free and 65% were alive. Among those with an initial remission more than 18 months, 57% were failure-free. The results of high-dose therapy at first relapse in these two studies are encouraging, especially the remarkable freedom from progression or failure among patients with late relapses. However, longer follow-up will be needed to determine whether these favorable results persist over time and can be confirmed by others.

**Results of Randomized Trials**--The very good results with the use of high-dose therapy suggest that this modality represents a significant advance in the treatment of relapsed Hodgkin’s disease. However, some patients may have done well with conventional treatment strategies. In addition, patients who have undergone high-dose therapy are selected so as to exclude those not likely to tolerate or benefit from the treatment. Clearly, the best way to account for patient selection and differences in the distribution of prognostic variables among populations of study patients is with a randomized clinical trial. However, few randomized trials have addressed this question. The British National Lymphoma Investigation undertook such an endeavor [32]. To be eligible for the trial, patients had to satisfy the following criteria for high-risk disease: (1) failure to achieve a complete response to MOPP chemotherapy; (2) failure to achieve a complete response to an alternating or hybrid regimen, or relapse within 12 months after such a regimen; or (3) failure to respond to two or more treatment regimens. (These criteria define patients with a more unfavorable prognosis, compared to patients in first relapse after attaining a complete response.)

A total of 40 patients were randomized to receive either one course of BEAM (BCNU, etoposide, Ara-C, and melphalan) with autologous bone marrow support or up to three courses of BEAM at reduced doses (mini-BEAM) that did not require bone marrow support. At a median follow-up at 34 months, both event-free and progression-free survival were significantly improved in the high-dose chemotherapy with autologous bone marrow transplantation group, compared to the lower-dose treatment group. Overall survival was also higher in the group given bone marrow support, but the difference did not reach statistical significance.

This study supports the contention that higher doses of therapy with autografting improve the early outcome of patients with relatively unfavorable characteristics. Longer follow-up is required to determine whether an advantage in overall survival is realized, since changes in overall survival typically lag behind changes in event-free survival. The study also dramatizes an impediment to conducting randomized trials involving high-dose therapy and autografting: Patient accrual became very difficult in the second year of the study because patients refused to be randomized to the conventional treatment group.

**Retrospective Analyses**--Other authors have used retrospective methods to estimate the efficacy of high-dose therapy and autografting as salvage therapy. Lohri et al [19] analyzed a group of 71 patients in first remission treated with curative intent between 1970 and 1988. Sixteen of these patients received high-dose chemotherapy and autologous bone marrow at the time of relapse. Sequential univariate analysis identified B symptoms at relapse, time to relapse of less than 1 year, and original stage IV disease as most predictive of poor survival. The presence of one negative risk factor was the major determinant of outcome irrespective of the type of salvage treatment. Patients with no risk factors did as well with irradiation or doxorubicin-based chemotherapy as with high-dose chemotherapy and autologous bone marrow support. However, the small sample size limits the conclusions that can be drawn from this study.

Yuen et al [33] from Stanford University described the outcome of 60 patients who were refractory to
initial treatment or were in first relapse after combination chemotherapy and who received high-dose therapy with autografting. These patients were compared to a matched group of 109 patients treated with conventional salvage therapy. At 4 years of follow-up, event-free survival was nearly double in the group that received high-dose therapy than in the conventional-therapy group (50% vs 25%, \( P < .01 \)) and overall survival was greater (55% vs 46%, \( P = .24 \)). However, the differences between groups decreased (and were not statistically different) when only those with sensitive disease at relapse were considered.

Cox regression analysis identified high-dose therapy, a long duration of remission, and sensitivity of disease at relapse as predictive of event-free survival. The only factor predictive of overall survival was sensitivity of disease at the time of salvage or cytoreductive (prior to high-dose) treatment.

**Timing of Therapy**—The preceding discussion has dealt primarily with the question of whether high-dose therapy is more effective than conventional treatments. Much of the data would suggest that results with high-dose therapy are most likely better than results with conventional treatments. A related consideration is not whether, but rather, when and where to use high-dose therapy. This question of strategy takes into account other factors besides the efficacy of a particular treatment:

- Which patients are likely to benefit most?
- What other treatment options are available, and what outcome might be expected for a particular set of prognostic features?
- What are the short- and long-term side effects of a particular strategy?
- Should conventional therapy be used for patients with the most favorable characteristics at first relapse, with high-dose therapy reserved for subsequent relapses?

Chopra et al [34] reported on the results of 155 poor-risk Hodgkin's disease patients treated with high-dose BEAM and autologous bone marrow transplantation. Those in second or third relapse had a significantly better progression-free survival than those in first relapse.

Desch et al [35] used a decision analysis model to address the question of the timing of high-dose therapy. The hypothetical situation was of a young patient who relapsed less than 12 months after MOPP chemotherapy. The model suggested that the maximum benefit would obtained if high-dose therapy and autologous bone marrow transplant were used at second (as opposed to first) relapse or at second complete response. The estimated efficacy of conventional salvage therapy was critical in the model; if the situation was changed to relapse after initial treatment with a seven- or eight-drug regimen (with assumed poorer results from salvage chemotherapy), the optimal timing for high-dose therapy changed to first relapse.

This type of analysis provides a logical method by which different strategies can be compared and important factors can be identified. However, the accuracy of the calculated rank order of treatment strategies depends on the reliability of assumptions entered into the model. In some cases, the literature is unclear or there may be insufficient data. For example, the estimation of the efficacy of conventional salvage treatment after seven- or eight-drug primary therapy was made from a survey of nine expert oncologists because of a paucity of experience reported in the literature at the time. In summary, the question of strategic placement of high-dose therapy is difficult to answer short of well-designed clinical trials. Retrospective analyses can suggest when high-dose therapy may be more effective. Decision analysis is instructive but is limited by the validity and accuracy of assumptions entered into the model. Moreover, treatments may continue to improve as preparative regimens become better and as immediate and long-term morbidity and mortality are more carefully understood and avoided. Exciting results, such as those from Vancouver, where nearly two-thirds of patients were still in remission at 4-year follow-up, provide a strong rationale for using high-dose therapy at first relapse.

**Side Effects**—The long-term effects of treatment (leukemia and cardiac or other organ toxicity) decreased by about half the number of patients who experienced long-term survival after retreatment with MOPP chemotherapy. Similar concerns are being raised about high-dose therapy, even as short-term morbidity and mortality associated with high-dose therapy and transplantation has decreased significantly.

Specifically, several studies have suggested that high-dose therapy may accelerate the leukemogenic process. Traweek et al [36] reported an actuarial risk of 9% for clonal karyotypic abnormalities at 3 years after transplantation among patients with Hodgkin's disease or non-Hodgkin's lymphoma. The chromosomal abnormalities were characteristic of those reported for alkylating agent-related myelodysplastic syndrome (abnormalities of chromosome 5 or 7) and topoisomerase II-related (11q23 or 11q22) myelodysplastic syndrome. The mean time to
development of chromosomal abnormalities was 3.9 years after induction and 1.4 years after transplantation. Darrington et al [37] reported a cumulative incidence of myelodysplastic syndrome or acute myelogenous leukemia of 4% at 5 years after high-dose therapy for Hodgkin's disease, although 11% of those alive at the 5-year mark had myelodysplastic syndrome or acute myelogenous leukemia.

Clearly, further follow-up is needed to better characterize the risk of high-dose therapy-related leukemias, and to answer several related questions: Is the risk related to a particular preparative regimen? Is there a threshold of alkylator or topoisomerase exposure above which increased risk is seen? Should patients be treated earlier in the course of disease (ie, after first relapse) to decrease the cumulative exposure to alkylator therapy?

In summary, the use of high-dose therapy and autografting appears to represent a significant advance in the treatment of Hodgkin's disease patients in first relapse. These encouraging results, however, should be interpreted in light of the following concerns:

1. Longer follow-up is needed to determine whether improvements in disease-free survival translate into longer overall survival.
2. Patients who are given high-dose therapy may be highly selected and may have done well with conventional salvage strategies.
3. Longer follow-up is needed to characterize the long-term side effects of high-dose therapy.

**Recommendations**

Patients who relapse after radiotherapy alone should be treated with chemotherapy, and can be expected to fare as well as untreated patients. Patients who relapse early after chemotherapy and who have unfavorable characteristics are unlikely to do well with conventional salvage treatments, and should be considered for high-dose therapy. Patients with very favorable characteristics at first relapse may respond well to conventional second-line treatments, and it is unclear how much advantage high-dose therapy offers in this group. Patients should be treated on established research protocols aimed at improving the optimum high-dose therapy regimens and minimizing long-term side effects of treatment.

**References:**


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