Outcome of Treatment of First Relapse of Hodgkin's Disease After Primary Chemotherapy: Identification of Risk Factors From the British Columbia Experience 1970 to 1988

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The outcome of treatment for a first relapse of Hodgkin's disease after primary chemotherapy was analyzed in 80 patients. They were divided into four groups: group 1 (n = 24) had initially been treated with three cycles of (melchothrathamine, vincristine, prednisone, and procarbazine [MOPP]) and wide-field irradiation therapy; group 2 (n = 25) had six cycles of MOPP; group 3 (n = 15) and group 4 (n = 16) both initially received MOPP/ABVD (MOPP plus doxorubicin, bleomycin, vinblastine, and dacarbazine) or MOPP/ABV hybrid, but group 3 received conventional salvage regimens whereas group 4 was treated with high-dose chemotherapy and autologous bone marrow transplantation as salvage therapy (n = 16). Freedom from second failure (FF2F) was used as the major endpoint. Actuarial FF2F for all patients was 38% after a median follow-up of 75 months for patients who were alive. Risk factor analysis was performed on the 71 patients who had been treated with curative intent. The presence or absence of any one of three risk factors had a strong negative impact on outcome: stage IV disease at primary diagnosis, B symptoms at relapse, or a time from primary treatment to relapse of less than 1 year. Actuarial FF2F at 5 years was 17% in the group of patients with one or more of these three factors present (n = 49). If none of these factors was present, FF2F was 82% (n = 22) [P < .001]. Even high-dose chemotherapy and autologous bone marrow transplantation were not able to overcome the negative impact of one or more risk factors (FF2F = 19%, n = 12). The outcome of salvage treatments depends most on the presence or absence of these three risk factors and less on the type of salvage treatment. Patients with none of these risk factors present have an excellent outcome if they are treated with non-cross-resistant chemotherapy, or radiotherapy, or both. Novel approaches are needed for patients with one or more of these factors present. Reports on salvage treatments for Hodgkin's disease in first relapse after primary chemotherapy should include data on the proportion of patients having stage IV disease at diagnosis, B symptoms at relapse, and a time from primary treatment to relapse of less than 1 year.

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MORE THAN 80% OF PATIENTS with advanced Hodgkin's disease enter a complete remission (CR) after chemotherapy with MOPP (melchothrathamine, vincristine, prednisone, and procarbazine) or a seven- or eight-drug regimen such as MOPP/ABVD (MOPP plus doxorubicin, bleomycin, vinblastine, and dacarbazine). However, relapses occur in up to 40% of these patients and they require additional treatment. Patients relapsing after MOPP have commonly been treated with a doxorubicin-containing regimen and those relapsing after MOPP/ABVD have been treated with one containing etoposide. For selected patients who relapse in nodal sites only, extended field irradiation may be a curative option. Complete response rates up to 80% have been reported using doxorubicin-containing regimens for relapse after primary treatment with MOPP or in up to 44% of the patients with an etoposide-containing regimen after MOPP/ABVD. However, further follow-up shows that fewer than 30% and 20% of the respective groups remain in sustained second remissions.

Wishing to improve on the modest results with available salvage chemotherapy, investigators have turned to high-dose chemotherapy with autologous bone marrow transplantation (HDC/ABMT). These ABMT-based protocols have been offered to patients with primarily refractory disease or in first, second, or subsequent relapse. Complete response rates and early follow-up have been encouraging. However, the results reported in most ABMT series include patients who underwent the procedure for widely varying states of disease. While HDC/ABMT is probably the only potentially curative option available for patients who fail to enter an initial CR or for those in second or subsequent relapse after two or more separate courses with different multi-agent chemotherapy regimens, it is not clear from the available literature whether HDC/ABMT should be routinely recommended for patients in first relapse. Thus, additional data specifically focusing on the outcome of treatment of first relapse is needed to determine what factors most affect the efficacy of the second or salvage therapy used.

To better understand the outcome for patients administered various treatments for first relapse after primary chemotherapy, we examined our experience between 1970 and 1988 with patients relapsing after potentially curative primary chemotherapy. Such data should be useful in determining an optimal approach for patients with Hodgkin's disease who are not cured by their initial chemotherapeutic treatment and allow the identification of risk factors associated with particularly favorable or unfavorable secondary outcomes.
PATIENTS AND METHODS

Patients

To identify a study group of patients who had relapsed after initial treatment with potentially curative chemotherapy, we examined the records of all patients who received their primary treatment in the province of British Columbia between January 1, 1970 and July 1, 1988. These 1,170 patients represent a large majority of those found to have Hodgkin's disease in this province, where annual incidence varies between 50 and 80 new cases and currently averages about 70. Because different treatment strategies are used for children, the elderly (>65 years old) and those with major comorbid illnesses such as the acquired immunodeficiency syndrome, such patients were not included in this study. We identified a group of 80 patients who met these age and health criteria, had entered a CR after primary chemotherapy, and had later relapsed. Nine patients received palliative treatment for their relapse. The 71 patients treated with curative intent were further categorized into four groups on the basis of primary chemotherapy. Their characteristics are summarized in Table 1. Relapse was documented by biopsy if present in peripheral lymph nodes or the bone marrow. Otherwise, unequivocal new radiologic lesions were accepted as proof of relapse in the absence of another reasonable explanation.

Group 1 consisted of 21 patients treated according to a national protocol between 1974 and 1981 in which primary treatment consisted of three cycles of MOPP and moderate-dose wide-field irradiation (RT). Compared with the other groups, tumor burden was lower in this group, with more patients having stage II disease and few patients having B symptoms. Also, their median time to relapse was longer than those in the other groups. First relapses in this group occurred between 1976 and 1985, and doxorubicin-containing regimens were, in part, available to them. One patient is included who received three cycles of MOPP, but refused to be irradiated.

Group 2 consisted of 20 patients who were treated between 1970 and 1981 and received six or more cycles of MOPP. Six patients received additional radiation therapy (extended field, five patients; involved field, one patient). First relapses occurred between 1971 and 1982. Doxorubicin-containing regimens were available to only a few of these patients.

Group 3 consisted of 14 patients treated between 1979 and 1985 with six to eight cycles of MOPP/ABVD according to Bonadonna et al. (six patients) or MOPP/ABV-hybrid (eight patients). Three patients received additional extended-field radiation therapy. First relapses occurred between 1981 and 1988. This group did not receive HDC/ABMT either because of lack of availability or clinician choice. Three of these patients did have ABMT for a second relapse later in the course of their disease. They are included in this group because their first salvage treatment did not include ABMT.

In group 4, primary treatment was similar to that of group 3, but all 16 patients received HDC/ABMT as treatment for first relapse.

| Table 1. Characteristics of All 71 Patients Treated With Curative Intent |
|-------------------------|------------------|------------------|------------------|------------------|
| Group | 1 | 2 | 3 | 4 | Total |
| Primary chemotherapy | MOPP × 3 + RT | MOPP × 6 | MOPP/ABV (D) |
| No. of patients | 21 | 20 | 14 | 16 | 71 |
| Sex | | | | | |
| Male | 14 | 17 | 9 | 9 | 49 |
| Female | 7 | 3 | 5 | 7 | 22 |
| Median age at diagnosis | | | | | |
| (range) | (16-60) | (19-62) | (17-61) | (18-50) | (16-62) |
| B symptoms at diagnosis | | | | | |
| I | 2 | — | — | — | 2 |
| II | 10 | — | 3 | 4 | 17 |
| III | 6 | 8 | 7 | 6 | 27 |
| IV | 3 | 12 | 4 | 6 | 25 |
| Histology at diagnosis | | | | | |
| Nodular sclerosing | 14 | 8 | 10 | 14 | 46 |
| Mixed cellularity | 5 | 8 | 3 | 2 | 18 |
| Lymphocyte depleted | 2 | 2 | — | — | 4 |
| Lymphocyte predominant | — | — | — | — | — |
| Unspecified | — | 2 | 1 | — | 3 |
| Median time to relapse | | | | | |
| (range) | (4-78) | (3-72) | (3-46) | (3-55) | (3-78) |
| % Patients relapsing within <1 y | 43 | 35 | 50 | 69 | 48 |
| % Patients with B symptoms at relapse | 14 | 25 | 29 | 19 | 21 |
| % Patients with nodal relapse only | 67 | 65 | 79 | 75 | 70 |
| % Patients with relapses within a previously irradiated field | 71 | 15 | 7 | 38 | 35 |
| Median follow-up in mo for patients alive | 80 | 139 | 60 | 42 | 75 |
| (range) | (49-123) | (108-176) | (22-108) | (15-50) | (15-176) |

Patients are divided into four groups. Primary treatment of group 3 and 4 is similar, but the patients in group 3 were treated with conventional salvage regimens, whereas the patients in group 4 received HDC/ABMT as treatment of first relapse.
Six patients had received initial MOPP/ABVD. One patient had three cycles of MOPP, one cycle of ABVD, and total lymphoid irradiation. Nine patients had MOPP/ABV-hybrid, three of these with additional involved-field radiation therapy. One patient had six cycles of ABVD and mantle irradiation.

Treatments Given for Relapse

Other than for group 4, no specific salvage regimen was used. Treatment decisions were made individually and reflect the changing policies of the past two decades. The different salvage regimens were grouped as follows.

MOPP-based salvage regimens. These 20 patients received the MOPP regimen as their salvage treatment. In a few, mechlorethamine was replaced by chlorambucil or vincristine by vinblastine. Several patients had additional radiation therapy (n = 7).

Doxorubicin-based chemotherapy. Of these 18 patients, 17 received MOPP/ABV or MOPP/ABV-hybrid and one had ABVD only.

Extended-field irradiation. Irradiation, usually total nodal, was given with curative intent to 17 patients. Doses from 3,000 cGy to 4,500 cGy were administered in fractions of 150 to 200 cGy with standard specific-organ shielding as required. All patients in primary group 2 who received salvage irradiation were treated before 1980. In group 3, one was treated in 1981, two in 1984, four in 1985, and one in 1987.

HDC/ABMT support (group 4, n = 16). As part of their preparation for ABMT, 11 patients received at least two cycles of MVPP (mechlorethamine, vinblastine, procarbazine, and prednisone) and 11 patients received involved-field irradiation. The high-dose regimen was cyclophosphamide 1.8 g/m² intravenously (IV) on days 1 through 4, carmustine 600 mg/m² IV on day 5, and etoposide 400 mg/m² IV twice daily on days 1 through 3 or 2,408 mg/m² IV by continuous infusion over 34 hours starting on day 1. Autologous bone marrow previously harvested from the pelvis was rein infused on day 8. Complete details have been described elsewhere.30-32,34

Palliative treatment. In nine patients, mainly during the 1970s, no curative attempt was made and either single-agent chemotherapy or palliative irradiation was attempted secondarily.

Definition of Response and Statistical Analysis

A CR was defined as complete resolution of all initially abnormal findings. Re-evaluations were usually performed 1 to 2 months after the completion of treatment. In agreement with its common use, the term “salvage treatment” was used for any form of treatment for relapse with curative intent. Time to relapse was calculated in months from the date of the end of the primary treatment to the date of a documented recurrence. Second failure was defined as any one of the following: less than a CR after treatment for relapse, toxic death, or second relapse. Duration of freedom from second failure (FF2F) was measured in months from the date of first relapse to toxic death, second relapse, or last follow-up. If less than a CR was observed after salvage treatment for relapse, the duration of FF2F was considered to be zero. Overall survival was measured in months from the date of first relapse to death or last follow-up. Actuarial curves for OS and FF2F were plotted according to the method of Kaplan and Meier.35 Comparison of survival curves for statistical significance was performed using the log-rank test.36

RESULTS

From a total of 80 patients, 42 are alive (53%), 40 (50%) are disease free, 30 (37%) are in a continuous second CR, 10 (13%) are in a third or subsequent CR, and two are alive with disease. Fifty patients (63%) either never entered a second CR or failed to sustain it. Thirty-eight patients died (47%): two without disease, one of lung cancer in group 2 (counted as failure at the time of second relapse; he died in third CR) and one of toxicity in group 4.

Eight of the nine patients initially treated with palliative intent have died. For one patient, treatment policy later changed and he is now disease free 68 months after MOPP/ABV-hybrid for a third relapse.

For the purpose of a risk factor analysis, only the 71 patients treated for the first relapse with curative intent are included. FF2F for this entire group is shown in Fig 1. Forty-one patients (58%) are alive and 30 patients (42%) are in a continuous second CR. The actuarial projection indicates that a plateau in FF2F occurs at about 5 years from the date of first relapse. We have not observed any relapses or late toxic deaths beyond that point. For this reason, we chose to use a comparison of actuarial 5-year FF2F as the major end-point in this study.

We examined the impact of the presence or absence of various risk factors on outcome. The following factors had no significant impact on the outcome of treatment of a first relapse: sex, histology, B symptoms at initial diagnosis, use of laparotomy for initial staging, or age at relapse greater or less than 40 years. We found five factors that were prognostically significant in univariate analysis: B symptoms at relapse, time to relapse of less than 1 year after completion of primary chemotherapy, presence of extranodal disease at relapse, and relapse within a previously irradiated field. Sequential univariate analyses were used to determine the relative importance of these factors. Presence of B symptoms at relapse was most powerful followed in order by time to relapse and original stage IV disease. Once those three factors were accounted for no additional impact on prognosis was exerted by presence of extranodal disease at relapse or relapse within a previously irradiated field.

Table 2 shows the FF2F for subgroups of patients with various combinations of the three important risk factors. These data indicate that the presence of even one factor strongly affects outcome. This is also evident in Fig 2. If stage IV disease at diagnosis, B symptoms at relapse, or a
Influence of Risk Factors on Outcome for Different Primary Treatment Groups

The presence of a risk factor of stage IV disease at original presentation, B symptoms at relapse, or a time to relapse shorter than 1 year was a major determinant of outcome of salvage therapy. The impact of these factors was independent of the type of primary chemotherapy, as is shown in Table 3. For all three primary treatment groups (group 3 and group 4 are pooled together because their primary treatment was the same), the presence of one or more of the risk factors predicted a poor outcome of salvage treatment with FF2F, 27% or less. For patients whose primary treatment consisted of three cycles of MOPP and irradiation or MOPP/ABV(D), absence of all three risk factors correlated with excellent outcome (FF2F 89% and 88%, respectively). The lack of quite as good an outcome in the MOPP × 6 group is almost certainly due to unavailability of doxorubicin-based chemotherapy when the relapses were treated, as will be discussed below. Thus, the impact of presence of stage IV disease at presentation, B symptoms at relapse, or a short time to relapse was present regardless of type of primary treatment.

Impact of Risk Factors on Outcome of the Various Salvage Strategies for First Relapse

Four main salvage strategies were analyzed: curative irradiation therapy (n = 17), MOPP (n = 20), doxorubicin-based conventional regimens (n = 18), and HDC/ABMT (n = 16). Table 4 shows the impact of the three risk factors on outcome broken down by type of salvage treatment. Once again, the presence of at least one risk factor is the major determinant of outcome regardless of salvage approach. The one exception is instructive. Patients who received MOPP as salvage treatment mostly were drawn from the group who had had primary MOPP. Salvage with MOPP was unsuccessful for the majority of patients whether or not a risk factor was present. Thus, we were unable to confirm the previous observation that MOPP is a successful salvage treatment when relapse occurs more than 1 year after primary MOPP. This finding is in contrast to the effectiveness of doxorubicin-based chemotherapy when all three risk factors are absent (FF2F = 100%, n = 7) and accounts for the entire difference observed above when the primary treatment subgroups of MOPP × 3 + RT and MOPP × 6 are compared (see Table 3). The MOPP × 3 + RT patients without risk factors at relapse usually received doxorubicin-based chemotherapy (n = 6), and all of these who did responded well (FF2F = 100%). The MOPP × 6 subgroup without risk factors at relapse did not receive doxorubicin-based chemotherapy and did poorly.
To assess the potential usefulness of HDC/ABMT as salvage treatment for patients receiving the best currently available primary chemotherapy, we examined the outcome of salvage treatment for the 16 patients primarily treated with MOPP/ABV(D). Their FF2F is shown graphically in Fig 3 and strongly suggests that even such intensive treatment as HDC/ABMT is not able to overcome the adverse impact of the three factors we identified.

DISCUSSION

Reports on salvage treatment regimens for patients with Hodgkin’s disease relapsing after multi-agent chemotherapy generally show a poor outcome, with fewer than 30% of the patients remaining durably disease free. Risk factors such as B symptoms, time to relapse, or extranodal disease at relapse have been identified, but interpretation of their importance has been rendered difficult by the complexity of patient groups studied, which often include the whole spectrum of patients with primarily or secondarily refractory disease, and various primary chemotherapy regimens. We confined our analysis to examine the outcome after salvage treatment for first relapse after a primary chemotherapy-induced CR, focusing on FF2F, the measure which best describes the outcome after salvage treatment because it includes as negative outcomes failure to reach a second CR, toxic death, and second relapse.

In sequential univariate analyses, three risk factors were identified that had a strong predictive impact on outcome: initial stage IV disease, B symptoms at relapse, or a time to relapse of less than 1 year after completion of primary treatment. All three factors have been mentioned by others, but the strength of their predictive power was usually lost due to the small and heterogeneous patient groups described.

Analyzing the impact of these risk factors in all 71 patients treated with curative intent shows that if one of the risk factors is present, the FF2F rate decreases to 27% or less. Therefore, it is imperative to separate patients by presence or absence of these risk factors in any analysis comparing patients subjected to a specific salvage treatment.

Regardless of primary treatment regimen, the outcome for patients with a risk factor present is surprisingly similar, with about 20% being free from a second failure. If none of the risk factors is present, about 80% of the patients remain disease free provided they were treated with non-cross-resistant chemotherapy containing either doxorubicin or etoposide or wide-field irradiation. The patients who were primarily treated with MOPP × 6 stand out with a somewhat lower success rate, even if risk factors were absent. This can be explained by the analysis of the four main salvage strategies. As shown in Table 4, if risk factors were absent, patients did equally well whether they received radiation treatment, doxorubicin-based salvage regimens, or HDC/ABMT. We were unable to salvage patients as successfully with MOPP after primary MOPP chemotherapy even if they had no risk factors. Fisher et al described a CR rate over 90% in a similar patient group with more than 40% of the patients remaining disease free. Given our much more favorable results in patients treated with doxorubicin-based chemotherapy for relapse after MOPP × 3 + RT when risk factors were absent (FF2F = 100%), we assume that retreatment with MOPP is an inferior strategy, probably because of persistent chemotherapy resistant clones.

It was particularly revealing to examine the impact of the presence of the three risk factors, initial stage IV disease, B symptoms at relapse, or a short time to relapse on outcome when the salvage treatment consisted of HDC/ABMT. This was of special interest because such an approach is rapidly becoming standard for patients relapsing after primary chemotherapy. In our results, the presence of a risk factor strongly predicted outcome of salvage treatment even when HDC/ABMT was used. Whereas the FF2F was 75% for patients without risk factors, only 4 of 12 patients with a risk factor remain failure free and the actuarial projection decreases to 19% (Fig 3). Thus, we have not been able to show an improvement in outcome for poor-risk patients after intensive treatment supported by ABMT.

Another interesting result evident from our analysis is that patients can be successfully treated with extended-field irradiation even when disease relapses after MOPP/ABD(D)-type regimens. This confirms the observations of several other groups. However, we have been able to add the observation that such a radiation-based approach is likely to be successful only if the patient is free of the three risk factors we identified.

Our results indicate that the outcome of salvage treatment for patients with Hodgkin’s disease in first relapse after primary chemotherapy depends most on the presence or absence of three risk factors: initial stage IV disease, B symptoms at relapse, and time to relapse of less than 1 year.
Our interpretation of these findings cannot be considered conclusive given the retrospective nature of our analysis, the modest numbers of patients in various subgroups, and variable follow-up times. However, within these limits our data indicate that the presence of any one factor indicates low likelihood of successful salvage treatment, even with ABMT-supported protocols. Such patients should probably be treated with novel approaches, perhaps including ABMT, but additional potentially active new agents should also be introduced. Patients who had less than stage IV disease at presentation, were free of B symptoms at relapse, and relapsed more than 1 year after primary chemotherapy should receive non–cross-resistant chemotherapy, or radiotherapy, or both. If their disease is fully encompassable by extended-field irradiation, it offers an excellent chance of cure. If they cannot receive irradiation due to in-field relapse or extent of disease, non–cross-resistant chemotherapy can be used. Patients who relapse after primary chemotherapy and have one of the unfavorable factors we identified should be treated with novel approaches that maximize use of potentially non–cross-resistant agents and modalities. For example, such a patient relapsing after several- or eight-drug MOPP/ABV(D)-type chemotherapy should be given irradiation to nodal sites and HDC with etoposide, an alkylating agent, and other more experimental agents such as cisplatin in the highest possible doses using marrow transplantation and hematopoietic growth factors for supportive care. Finally, it is imperative that those reporting results of salvage treatment with ABMT support indicate what proportion of transplanted patients had initial stage IV disease, B symptoms at relapse, or a short time to relapse. Without such data, their results cannot be usefully interpreted.

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