Intensive therapy and autotransplant for patients with an incomplete response to front-line therapy for lymphoma


University of Toronto Autologous Blood and Marrow Transplant Program, The Toronto Hospital, Toronto, Ontario, Canada

Summary

Background: Patients with Hodgkin’s disease (HD) and intermediate or high-grade non-Hodgkin’s lymphoma (NHL) who fail to achieve a complete remission (CR) with standard induction therapy have a poor prognosis with conventional-dose salvage therapy alone. We examined the role of subsequent intensive therapy and autologous bone marrow transplantation (ABMT) in patients who demonstrated a response to conventional-dose salvage therapy.

Patients and methods: Sixty-six patients with either HD (n = 30) or NHL (n = 36) underwent intensive therapy with etoposide (60 mg/kg), intravenous melphalan (160–180 mg/m²) followed by infusion of unpurged autologous bone marrow and/or blood cells. All patients had advanced stage or bulky disease at diagnosis and failed to achieve a CR after an anthracycline-containing front-line chemotherapy regimen (NHL) or ABVD or equivalent regimen (HD). Patients who achieved a CR after involved-field radiotherapy were excluded. All patients demonstrated sensitivity to conventional-dose salvage treatment before advancing to intensive therapy and ABMT.

Results: The CR, partial response (PR) and overall response rate (RR) following ABMT for HD patients was 48%, 17% and 65%, respectively. At a median follow-up of 35 months, the predicted three-year overall survival (OS) is 51% (95% CI: 44%–60%) and event-free survival (EFS) is 34% (95% CI: 26%–54%). For patients with NHL, the CR, PR and RR were 68%, 9% and 77%, respectively. At a median follow-up of 28 months, the predicted three-year OS is 51% (95% CI: 35%–66%) and EFS is 39% (95% CI: 21%–57%).

Conclusions: Intensive therapy with etoposide and melphalan followed by ABMT results in prolonged survival in selected patients with lymphoma who fail to achieve a complete remission to front-line chemotherapy. Based on our previous studies of outcome to conventional-dose salvage chemotherapy, we estimate that of all patients failing induction therapy, 28% with HD and 15% with NHL will be event-free at three years after ABMT.

Key words: induction failure, Hodgkin’s disease, non-Hodgkin’s lymphoma, refractory lymphoma

Introduction

Induction chemotherapy for advanced stage Hodgkin’s disease (HD) results in complete remission (CR) in approximately 60% to 85% of patients [1, 2]. However, for those who fail to achieve CR following ABVD or similar front- or second-line regimens the outlook is poor. Only 15% to 30% obtain a complete remission with subsequent salvage treatment and approximately 80% of this group will relapse. Indeed, for the remaining patients who never enter CR with subsequent salvage therapy, less than 5% are long-term survivors [3–14]. Although involved field radiation is beneficial in limited stage HD, less than 10% of patients with advanced disease can be salvaged with this therapy [15, 16]. Similarly, for patients with intermediate grade or immunoblastic non-Hodgkin’s lymphoma (NHL), 30%–45% with advanced stage disease will fail induction therapy [17]. Although subsequent conventional-dose salvage therapy leads to complete remission rates of 7% to 27%, only 5%–25% have a sustained remission, resulting in less than 10% of all patients who fail induction therapy remaining disease-free [18–24].

The role of intensive therapy followed by autologous bone marrow transplantation (ABMT) for HD and NHL has focused primarily on patients who relapse after an initial CR. Although, randomized trials comparing ABMT to conventional-dose salvage therapy have demonstrated a benefit in those patients who undergo ABMT in this setting [25, 26], the role of ABMT for patients who fail induction therapy requires further investigation. On the basis of the poor results of ABMT in patients who are refractory to conventional-dose salvage therapy, demonstrable chemotherapy sensitivity was a prerequisite for eligibility for these trials.

We previously demonstrated the efficacy of high-dose etoposide and melphalan in patients with chemotherapy-sensitive relapsed HD [27] and NHL [28]. We now further examine the efficacy of this regimen in patients with an incomplete response to front-line anthracycline-containing chemotherapy who demon-
strated chemotherapy sensitivity to conventional-dose salvage therapy, a group otherwise unlikely to be cured with conventional-dose salvage therapy alone.

Patients and methods

Sixty-six consecutive patients referred to our center with lymphoma who failed primary therapy and subsequently underwent ABMT were included for analysis in this study (Tables 1 and 2).

Front-line therapy

To be eligible for this study all patients were required to have biopsy proven HD \((n = 30)\) or intermediate or high grade NHL at diagnosis according to the International Working Formulation and confirmed by central pathological review. All NHL patients \((n = 36)\) were treated with an anthracycline-containing regimen at diagnosis. Similarly, patients with HD had received ABVD or similar chemotherapy regimens. All patients failed to achieve a CR or had progressed (NHL: \(n = 5\), HD: \(n = 7\)) during initial therapy; six patients with HD had also received and failed second-line therapy (Table 1). In order to exclude patients who were potentially curable with radiation alone, any patient referred to our center who had an incomplete response to chemotherapy but had achieved CR after subsequent involved-field radiotherapy were deemed ineligible. Such patients only underwent autotransplant at the time of disease progression and have been previously reported [27, 28].

Diagnosis of persistent disease after front-line therapy

Most patients were referred to our center for consideration of ABMT because of persistent radiological abnormalities following initial chemotherapy. Persistent disease was determined by a repetitive biopsy whenever possible \((n = 44; 67\%)\). In the cases where clear radiological progression was documented or measurable lesions remained unchanged on CT scan, no biopsy was performed \((n = 7; 10\%)\). Persistent disease was also defined by an abnormal CT scan together with either a positive gallium scan \((n = 12; 18\%)\) or elevated lactate dehydrogenase (LDH) (>3× normal) \((n = 3; 5\%)\).

Conventional-dose salvage therapy

Sensitivity to conventional-dose salvage therapy (>50% reduction in the product of the longest diameter and perpendicular diameter of measureable lesions) was a prerequisite for ABMT. Patients not meeting these response criteria after two cycles of salvage chemotherapy were treated with an alternative regimen, and in some instances, radiotherapy. Those who failed to achieve at least a partial response with this therapy were considered resistant and were excluded from intensive therapy and autotransplant [3, 29] (NHL: \(n = 43\), HD: \(n = 10\)). These patients were treated at the discretion of their referring physician and are not included in this analysis. Other eligibility criteria included age 18–61 years, absence of serious underlying medical illness, negative HIV-1 serology, normal renal, pulmonary, cardiac and liver function and ECOG performance status of ≤2.

Table 1. Characteristics and treatment regimens of patients with Hodgkin’s disease \((n = 30)\).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median age (range)</th>
<th>Gender (male/female)</th>
<th>Stage</th>
<th>Histology</th>
<th>Front-line therapy</th>
<th>Second-line therapy</th>
<th>Salvage therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>28 (17–48)</td>
<td>19/11</td>
<td>I</td>
<td>Nodular sclerosing</td>
<td>ABVD</td>
<td>MOPP/ABV±D</td>
<td>DHAP</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td></td>
<td></td>
<td>II</td>
<td>Mixed</td>
<td></td>
<td></td>
<td>miniBEAM</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td>III</td>
<td></td>
<td></td>
<td>MOPP/ABV</td>
<td>CVP</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td>IV</td>
<td></td>
<td></td>
<td>MOPP + ABVD</td>
<td>Other</td>
</tr>
<tr>
<td>Front-line therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VACOP/B</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACOP/B</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'ALL'</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROMACECytaBOM</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHAP</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miniBEAM</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVP</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Does not include mantle cell lymphoma.

Abbreviations: CHOP – cyclophosphamide, adriamycin, vincristine, prednisone; VACOP/B – etoposide, adriamycin, cyclophosphamide, vincristine, prednisone ± bleomycin; MACOP/B – methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone ± bleomycin; 'ALL' – acute lymphoblastic leukemia like protocol containing adriamycin, vincristine, cyclophosphamide, prednisone, methotrexate; PROMACECytaBOM – prednisone, vincristine, methotrexate, adriamycin, cyclophosphamide, etoposide, cytosine arabinoside, bleomycin; CVP – high dose cyclophosphamide (4–7 g/m²), vincristine, prednisone.
Staging prior to ABMT

Complete restaging was performed immediately prior to ABMT and included chest radiograph, CT scans of thorax, abdomen and pelvis, bone marrow aspirate and biopsy in all patients; and gallium scan, bone scan and LDH if previously abnormal. Complete remission required the absence of all clinical, radiological and biochemical evidence of disease for a minimum of 30 days and until the time of transplant. All patients undergoing autotransplant had tumours of <5 cm diameter immediately prior to ABMT.

Autograft collection

Bone marrow free of disease by histological examination was harvested, processed and stored as previously described [30]. Patients with marrow involved with lymphoma (<15%) of marrow nucleated cells had blood cells (BC) collected after mobilisation with cyclophosphamide (4 or 7 g/m²) and GM-CSF (5 μg/kg/day) (Sandoz, Canada). Some patients who lacked an adequate BM harvest (<1.5 x 10⁹ nucleated cells/kg) for reasons other than BM involvement with lymphoma, received BCs alone or in combination with the BM. Purging of the BM or blood cells was not performed.

Intensive therapy

Chemotherapy at the time of ABMT comprised intravenous etoposide (60 mg/kg) on day -4 and melphalan (160 or 180 mg/m² intravenously) given on day -3. In addition, patients with small non-cleaved Burkitt’s lymphoma and peripheral T-cell NHL received total body irradiation 1200 cGy administered in six fractions of 200 cGy twice daily starting day -2 at a mean rate of 60 cGy/min (range: 40–90 cGy/min). On day 0, the cryopreserved autograft was thawed at 40 °C in a waterbath at the bedside and infused rapidly through a central venous catheter. Patients received standard supportive care and most received GM-CSF during the period of neutropenia.

Follow-up

Only patients with a minimum of 12 months follow up from the time of transplantation are included in this analysis. Patients were completely restaged three months after ABMT to establish response to intensive therapy, then at three monthly intervals for the first year, six monthly intervals in the second year and yearly thereafter. Patients transplanted in CR who remained in CR and patients transplanted in PR who showed improvement or no change in residual imaging abnormalities without other evidence of disease for a minimum of six months were defined as event-free.

Statistical analysis

Both overall survival (OS) and event-free survival (EFS) were analysed from the day of transplant. All patients dying from any cause were included in the overall and event-free survival analysis. Survival curves were generated using the method of Kaplan and Meier and compared using log-rank analysis. A Cox proportional hazards model was used to analyse the contribution of the following potential prognostic variables on EFS and OS: age, gender, stage, extranodal disease, bulky disease (> 10 cm), 'B' symptoms at diagnosis, number of prior chemotherapy cycles, progression during front-line therapy versus incomplete response, and remission status immediately prior to transplant. The small number of patients in each lymphoma cohort prohibited a statistically valid multivariate analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, Version 6.1)

Results

Patient characteristics and pre-transplant therapy

Characteristics of the 66 patients treated with intensive therapy and ABMT are provided in Tables 1 and 2. The median time from diagnosis to transplant was 15 months (range: 5–50) and the median time from last salvage treatment to transplant was two months (range: 1–6).

Hodgkin’s disease

Nineteen males and 11 females with a median age of 28 years (range: 17–48) were included in this analysis. (Table 1) Patients had bulky stage IA (n = 3), IIb (n = 7) or more advanced disease (n = 20) at diagnosis. All had failed an anthracycline-containing front- or second-line regimen. Front-line therapy consisted of either ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) (n = 11), MOPP (mechlorethamine, vincristine, procarbazine, prednisone) (n = 3), MOPP/ABV(+/−D) (n = 12), or VECABOP (vinblastine, etoposide, cyclophosphamide, doxorubicin, bleomycin, vincristine, prednisone (n = 4)). Twenty-three patients had an incomplete response and seven patients demonstrated tumour progression during this therapy.

Six patients received one or two courses of second-line salvage chemotherapy consisting of ABVD (n = 1), MOPP (n = 2), MOPP/ABV (n = 1) or MOPP and ABVD (n = 2). An additional six patients with residual disease also received involved field radiotherapy but failed to achieve CR. Two patients with biopsy proven persistent HD following second-line therapy refused further immediate therapy for nine and 11 months and both experienced disease progression during the interval. The remaining patients (n = 28) proceeded directly to further salvage therapy prior to ABMT. The most frequently administered salvage regimens were DHAP (dexamethasone, cytosine arabinoside, cisplatin) [19] and miniBEAM (BCNU, etoposide, cytosine arabinoside, melphalan) [22]. The median number of cycles of salvage therapy was three (range: 2–8). Seventeen patients received local-field radiation therapy to sites of disease still detectable after salvage chemotherapy (Table 1).

Non-Hodgkin’s lymphoma

Twenty-three males and 13 females with a median age of 45 years (range: 19–61) were analysed. All patients received an anthracycline-containing front-line regimen to maximum response (Table 2). Five patients progressed during this therapy and in these cases conventional-dose salvage chemotherapy was commenced prior to the completion of the induction therapy regimen. The remaining 31 patients completed all cycles of induction therapy to maximum response before commencing salvage therapy. The most frequently administered salvage regimens were DHAP and miniBEAM, with a median of three cycles (range: 1–5) given to
maximum tumour reduction. Seventeen patients additionally received local-field radiation therapy. The three patients who received only one cycle of salvage therapy all developed marked myelosuppression with the salvage regimen and received local radiation rather than alternative salvage chemotherapy before ABMT.

**Engraftment and toxicity following ABMT**

The autograft product was BM (HD n = 27; NHL n = 23), blood cells (HD n = 1; NHL n = 5) or both (HD n = 2; NHL n = 8). Transplant-related mortality (TRM) for patients with HD and NHL was 20% and 14%, respectively. For all patients, the median time to absolute neutrophil count >0.5 x 10^9/l was 17 days (range: 9–63) and median time platelet count >20 x 10^9/l was 25 days (range: 8–380). The median length of hospital stay was 26 days (14–77).

**Outcome following ABMT**

**Hodgkin's disease**

Staging investigations prior to ABMT demonstrated no evidence of disease in seven patients. Of the remaining 23 patients, post-transplant remission status was evaluable in 20 (early TRM in three patients). Five of the 23 had stable disease (22%), four achieved a further reduction in tumour size (17%) and 11 (48%) obtained a CR for an overall response rate of 65%. At a median follow-up post-transplant of 35 months for all surviving patients (range: 9–91 months), the predicted three year survival is 51% (95% CI; 44–60) and the median survival has not been reached (Figure 1a). The corresponding predicted event-free survival (EFS) is 34% (95% CI; 26–54) with a median EFS of 19 months (Figure 1b). There have been two late, non-relapse related deaths; secondary acute myeloid leukaemia at 19 months post-ABMT and chronic active hepatitis due to hepatitis-B infection at 82 months post-ABMT. Univariate analysis failed to identify any single factor as a predictor of outcome after transplant.

**Non-Hodgkin’s lymphoma**

Fourteen patients were in CR and 22 in PR at the time of transplant. Of the 22 patients in PR at transplant, post-transplant remission status was evaluable in 20. Three had stable disease (13%), a further two achieved a PR (9%) and 15 a CR (68%), with a total response rate of 77%. At a median follow-up post-transplant of 28 months for all surviving patients (range: 9–84 months), the predicted three-year overall survival is 51% (95% CI; 35–66) (Figure 2a) and EFS is 39%

![Figure 1. Kaplan–Meier estimates of (a) overall survival and (b) event-free survival of patients with Hodgkin's disease (n = 30).](image1)

![Figure 2. Kaplan–Meier estimates of (a) overall survival and (b) event-free survival of patients with non-Hodgkin's lymphoma (n = 36).](image2)
survival following subsequent intensive therapy and induction therapy but remained sensitive to front-line therapy [40]. In this study, we demonstrated that these patients have a similar outcome following CR to front-line therapy. We excluded such results to those reported here for a cohort of thirty HD patients from this analysis as we have previously demonstrated remission status at transplant (P = 0.02) and B-symptoms at diagnosis (P = 0.03) as predictive of survival.

No difference in EFS was identified between patients who had biopsy proven persistent lymphoma (n = 44) and those who had only CT scan evidence of persistent disease (all associated with abnormal LDH or gallium scan) (n = 22; P = 0.36). Similarly there was no difference in outcome between patients who received blood cells, marrow or both as the autograft product (P = 0.64); however, only six patients received blood cells alone.

Discussion

None of the patients in this analysis were likely to be cured with conventional-dose salvage therapy alone. Patients had advanced stage and/or bulky disease and all with HD had failed ABVD or equivalent regimen, while all patients with NHL had failed an anthracycline-containing front-line therapy. Furthermore, patients with benign radiographic abnormalities and those who obtained CR with additional involved-field radiotherapy only underwent transplant at the time of further progression [27] and were excluded from this analysis.

Previously published studies of ABMT for patients with HD provide some evidence that an improvement in outcome may be obtained for patients who fail induction therapy. However, the number of subjects reported is small and the patients who failed induction therapy comprise only a subset of those studied [27, 31–36]. Reece et al. recently demonstrated similar results to those reported here for a cohort of thirty HD patients who failed induction therapy and underwent subsequent intensive therapy with cyclophosphamide, BCNU, etoposide +/- cisplatin and ABMT [37]. Some previous series examining ABMT following induction failure have included patients who relapsed up to a year following CR to front-line therapy. We excluded such patients from this analysis as we have previously demonstrated that these patients have a similar outcome following ABMT to patients who relapse beyond one year after induction treatment [27].

Despite the demonstrated superiority of ABMT over conventional-dose salvage chemotherapy in patients with relapsed NHL [26], the value of ABMT early in the treatment of NHL is unproven. ABMT does not appear to confer a survival advantage when used as consolidation therapy following first CR [38, 39] or for those patients who are slow to respond to front-line therapy [40]. In this study, we demonstrated that one third of patients with HD or NHL who failed induction therapy but remained sensitive to conventional-dose salvage chemotherapy achieve long-term survival following subsequent intensive therapy and ABMT. Indeed, such HD patients achieved a predicted EFS of 34% and patients with NHL treated with the same intensive therapy, with the addition of TBI in selected cases, had a 39% three-year EFS. This outcome is very similar to that of patients with NHL who undergo ABMT for chemotherapy-sensitive relapsed disease [28].

Since our cohort of patients was selected for ABMT after demonstrating sensitivity to conventional-dose salvage chemotherapy, this report does not address the value of ABMT in patients with lymphoma whose tumors are completely refractory to chemotherapy. Not unexpectedly, the previously reported 14%-17% EFS for such HD patients is half that reported here [41, 42]. Determining the proportion of patients failing induction therapy that may benefit from ABMT is a difficult task for transplant centers; referral bias and specific program eligibility criteria are confounding factors. This assessment is further complicated by patient referrals to our center from four provinces in Canada [30]. However, in previous studies of salvage therapy, we showed that 82% of HD patients [3] and 39% of subjects with non-Hodgkin's lymphoma [29] who fail induction therapy have disease that is sensitive to conventional-clone salvage chemotherapy. Taken together, our results suggest that of all patients failing induction therapy, 28% of subjects with HD and 15% of those with NHL have a projected three-year EFS after autotransplant.

The procedure-related mortality with this intensive therapy regimen is consistent with other ABMT studies in patients with resistant or early relapsed disease [34–36] and should be considered in the context of the poor prognosis of this group. However, longer follow-up is required to determine the number of patients who experience late relapse or develop treatment-related myelodysplastic syndromes (MDS) and/or acute myeloid leukemia. The latter are particularly relevant as ABMT was performed soon after front-line therapy and secondary MDS typically develops five to six years after primary treatment [43].

We conclude that intensive therapy and ABMT is effective and currently the most appropriate therapy for lymphoma induction failures who remain chemotherapy-sensitive. Further improvements in survival may result from a reduction in transplant-related toxicity.

References


43. Darrington DL, Vose JM, Anderson JR et al. Incidence and characterization of secondary myelodysplastic syndrome and acute myelogenous leukemia following high-dose chemoradio-


Received 21 August 1996; accepted 23 October 1996.

Correspondence to:
Dr. M. Crump
The Toronto Hospital
200 Elizabeth St.
miw 2-018
Toronto, Ontario
Canada M5G 2C4