review articles

Outcomes of Refractory and Relapsed Hodgkin Lymphoma With Autologous Stem-Cell Transplantation: A Single Institution Experience

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abstract

PURPOSE Hodgkin lymphoma is the most common cancer in children, adolescents, and young adults. Overall survival is approximately 80% to 90%. A subset of these patients has refractory disease or experience disease relapse. Conventional salvage therapies and autologous stem-cell transplantation is usually considered the standard of care for these patients. Our analysis reports outcomes in these patients.

PATIENTS AND METHODS After institutional review board approval, a retrospective analysis of patients with Hodgkin lymphoma who were up to 18 years of age and who had refractory or relapsed disease at Shaukat Khanum Memorial Cancer Hospital and Research Centre from September 2009 to December 2013 was performed. Patients who underwent high-dose chemotherapy followed by stem-cell rescue were included in this analysis.

RESULTS A total of 567 patients with Hodgkin lymphoma registered at the hospital. Sixty of the patients (10.6%) had either primary progressive or refractory disease or relapse after finishing with first-line chemotherapy. High-dose chemotherapy followed by stem cell was administered to 25 of these patients (42%). Thirteen patients (40%) had progressive disease (PD), five (22%) had early relapse, and seven (38%) had late relapse. A number of salvage regimens were used, including etoposide, prednisolone, ifosfamide, and cisplatin; dexamethasone, cytarabine, and carboplatin; and gemcitabine plus vinorelbine. Re-evaluation was performed before taking patients to a high dose, and it showed complete response in 17 patients (68%), partial response in six patients (24%), and PD in two patients (8%). Twenty-one patients (84%) are in remission after transplantation, with two patients (8%) having died as a result of disease progression and two patients (2%) having relapsed after treatment. Overall survival is 92% at 4 years, with event-free survival of 80% at 4 years.

CONCLUSION Our retrospective analysis shows good outcomes in patients who had PD or refractory disease. Disease response before transplantation is important in predicting outcomes.

INTRODUCTION

Hodgkin lymphoma (HL) is a common cancer in children, adolescents, and young adults, with a peak incidence between the ages of 20 and 34 years.[1] With the use of chemotherapy alone or with the addition of radiotherapy, the overall survival (OS) rate of newly diagnosed HL is approximately 80% to 90%. However, subsets of these patients with HL relapse or have refractory disease to first-line therapy. High-dose chemotherapy (HDC) followed by autologous stem-cell transplantation (auto-SCT) has been used in many patients with relapsed or refractory HL. HDC and auto-SCT are common practices for adult patients with relapsed and refractory HL.[2,3]

Most of the reported data in the literature pertains to adults rather than to the pediatric population. The few reported pediatric series available have a limited numbers of patients. Therefore, there are limited prospective scientific data in children (< 14 years) and adolescents (14 to 21 years) receiving HDC followed by auto-SCT, so it is unclear if children and adolescents would benefit the most with this strategy. Several studies have suggested extrapolating data on the benefit of HDC and auto-SCT from the literature on adults.[4-7] The aim of this study was to evaluate the outcomes of children and adolescents with relapsed or refractory HL treated with HDC and auto-SCT at our institution. In a resource-limited setting such as ours, outcomes were analyzed in progressive HL to decide whether to continue to offer this mode of therapy to patients. In this way, data on HDC and auto-SCT could be added to data that are limited in our part of the world. Disease response before transplantation is important, and OS is

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92% at 4 years, with event-free survival (EFS) of 80% at 4 years. Efforts must be made to provide this mode of treatment to all patients, even in resource-limited settings.

PATIENTS AND METHODS

This retrospective study took place at Shaukat Khanum Cancer Memorial Hospital, Lahore, Pakistan. Medical records were reviewed of those patients with primary progressive disease (PPD), who experienced early and late relapsed HL and went on to have HDC followed by auto-SCT. The patients' analyses were performed between January 2009 and December 2013. Data were collected on each patient's age, sex, stage at time of relapse, chemotherapy regimens, radiologic assessments at different intervals, and outcomes at the end of treatment and at last follow-up visit. Each patient's record was also reviewed for acute and long-term toxicity at the last follow-up visit. The institutional review board at the hospital approved the study.

PPD was defined as disease progression occurring in known disease and new sites of disease within 3 months of the initial planned treatment. Early relapse was defined as recurrence between 3 and 12 months after finishing first-line treatment. Late relapse was defined as recurrence 12 months after first-line therapy. Only those patients who went on to have HDC chemotherapy followed by auto-SCT were included for analysis.

Different salvage regimens were used before performing HDC. Stem-cell mobilization and harvesting were performed after the second or fourth cycles of chemotherapy, depending on feasibility. The three regimens used were EPIC (etoposide 100 mg/m^2 day 1 to day 4, prednisolone 60 mg/m^2 day 1 to day 5, and ifosfamide 1 g/m^2 day 1 to day 5, together with mesna plus hydration and cisplatin 60 mg/m^2 on day 10), GV (gemcitabine 1 g/m^2 on day 1 and day 8 and vinorelbine 25 mg/m^2 on day 1 and day 8), and DHAC (dexamethasone 40 mg/m^2 day 1 to day 4, cytarabine 2 g/m^2 on day 2, and carboplatin 600 mg/m^2 on day 2).

All imaging performed at relapse or progression and then at reassessment was positron emission tomography (PET) scan based. PET scanning was performed after the second and fourth cycles of salvage chemotherapy, depending on response and before taking the patient for HDC. Stem cells were harvested during the third cycle of chemotherapy and were stored in a blood bank to maintain their viability. The end of the auto-SCT imaging response was performed at day 60 (midway between day 30 and day 100) because of the limited resources in our part of the world.

PET computed tomography (CT) using ^{18}F-labeled fluorodeoxyglucose (^{18}F-FDG PET-CT) was used on the basis of standardized uptake values. A positive FDG-PET-CT was defined as a focal or diffused area of increased activity in an area incompatible with normal anatomy and physiology when residual disease was suspected by visual assessment. A negative PET scan indicated complete metabolic response.

Complete response was defined as complete resolution of all disease, partial response (PR) as $>$ 50% reduction, nonresponse or stable disease as less than PR, and progressive disease (PD) as the appearance of any new lesion or a $>$ 25% increase in the presence of a previous lesion or the appearance of disease-related symptoms. Refractory disease was defined in the same way as PR, nonresponse, or stable disease, or PD after planned multi-agent chemotherapy with or without radiation therapy or relapsing within 3 months of finishing the planned treatment after achieving a complete response (CR) or a CR unconfirmed. Patients refractory to salvage chemotherapy were labeled as refractory relapse.

The conditioning regimen used was BEAM (carmustine [BCNU], etoposide, cytarabine, and melphalan). In one patient, bendamustine was administered instead of BCNU because the patient had developed pulmonary toxicity with bleomycin as first-line chemotherapy. Patients were discharged home after count recovery. They were kept on close follow-up as outpatients after undergoing a scan after day 60, and regular cardiac, endocrine, and pulmonology evaluations were performed. Echocardiography was performed at 1 year after treatment, then at 3 years, and at the time of discharge from the cancer service. Pulmonology evaluation for lung toxicities was performed at 2 years after treatment and at the time of discharge. Regular height and weight measurements were taken at follow-up visits, and patients were referred to endocrinology clinics if there were any concerns. At discharge from the hospital, patients were given a detailed treatment summary and were advised of potential long-terms effects to watch out for and for which to seek immediate medical help.

SPSS software version 20 was used for all statistical analysis, including frequencies for demographics and median age and comparisons between variables, and Kaplan-Meier graphs for OS and EFS were plotted. OS was calculated as the percentage of patients who were alive at last follow-up, and EFS was defined as persistent disease, PD, or relapsed disease or death due any cause from day 0 or at last follow-up, whichever came first.

RESULTS

A total of 567 patients with HL registered for treatment between 2009 and 2013. Of the total, 60 (10.6%) had either PPD or early or late relapse. Most patients (20 [80%]) were $>$ 10 years of age; six were female.

Of the 60 patients who had either PD or relapse disease, 25 patients (42%) had HDC followed by stem-cell rescue (SCT), and the remaining 35 patients (58%) underwent salvage chemotherapy followed by radiotherapy to the involved area. Of these 35 patients, 19 had PD or early relapse for whom HDC was not administered. Clinical notes were reviewed to determine the cause; either the families

refused to allow this mode of treatment or sufficient stem cells could not be harvested and therefore, salvage regimens with radiotherapy were administered. Hence, these 19 patients were excluded from the analysis.

Of the 25 patients who had HDC followed by SCT, 13 had PPD, five had early relapse, and seven had late relapse. Of the seven late relapses, four patients had a second late relapse, one had progressed after being treated on second-line protocol for late relapse, and in two late relapses, auto-SCT was a physician decision at the time of relapse.

Relapse and disease progression were confirmed on rebiopsy, and complete restaging was performed before starting salvage chemotherapy. Staging at the time of disease progression and relapse is listed in Table 1. Multiple chemotherapy regimens were used as salvage before the patient received HDC. EPIC was used in 13 patients (52%), followed by GV in five (20%), and DHAC in four (16%), and three patients (12%) had EPIC followed by GV because they had disease progression but responded to third-line chemotherapy.

Reassessment scanning before HDC showed that 17 patients (68%) had CR, six patients (24%) had PR, and two patients (8%) had disease progression. The BEAM regimen was used in all patients with the exception of one patient who received bendamustine because he had developed pulmonary toxicity as a result of bleomycin being used as his first-line treatment. Patients tolerated the HDC well, and no acute complications were seen; patients were discharged after count recovery.

A repeat PET scan was performed at day 60 after HDC and SCT. Twenty-two patients (88%) were in CR, and three patients (12%) had disease progression. Of these three patients, two had refractory disease before HDC and auto-SCT. They later died as a result of respiratory complications of the disease in the mediastinum. The remaining patient with disease progression at the end of auto-SCT had radiotherapy to the involved areas and as of the last follow-up, she is alive and in remission. Table 2 lists the response of disease before HDC and then at day 60 according to the type of relapse.

The median survival time was 37 months (range, 9 to 74 months). On last follow-up, 21 patients (84%) were alive and in remission, two patients (8%) had died as a result of disease progression, and two patients (8%) relapsed but are alive and on palliation. Table 3 lists outcomes according to type of relapse. At 4 years, OS is 92% and EFS is 80% (Fig 1). No long-term complications were noted on the last follow-up date.

DISCUSSION

Outcomes in pediatric HL have improved in recent years with chemotherapy alone, and most patients remain disease-free, with longer survival rates. Approximately 15% of patients have PPD or refractory disease or relapse. Our analysis reports 10.6% of patients having PPD or relapse. Patients can be cured with second-line salvage chemotherapy and with HDC followed by auto-SCT.

There is a scarcity of pediatric data with reference to HDC and STC in HL from developing countries. There are no randomized trials to compare auto-SCT and second-line salvage chemotherapy in the pediatric population; much of the evidence is from adult studies and a few retrospective pediatric studies. In one randomized analysis between BEAM and auto-SCT versus mini-BEAM chemotherapy, the EFS at 3 years was 53% versus 10%.[8]

Another adult study showed freedom from treatment failure to be superior in patients randomized to the auto-SCT arm at 3 years, at 55% versus 34%.[9] Outcomes in relapsed or refractory pediatric HL treated with auto-SCT were studied in the ST-HD-86 trial, in which 53 of 176 patients underwent auto-SCT and 10-year OS was 51%.[6] Other pediatric studies have reported outcomes with a 5-year EFS ranging from 45% to 65% and 5-year OS from 55% to 74%.[10-15]

In our cohort of patients, EPIC, DHAC, and GV chemotherapy regimens were used, and the response was 98% (CR, 68% and PR, 24%), with only two patients who still had refractory disease before being taken for HDC and auto-SCT. Individual numbers are too small for analysis, but this study shows that the different salvage regimens used showed good response in both relapsed and refractory disease. Our analysis has this limitation because of the number of different salvage regimens used, and it is difficult to analyze the superiority of any one of them. There are no randomized trials of the best salvage regimen to use, but the overall response rates of a number of second-line chemotherapy regimens are well above 65% (mini-BEAM, 84%; ESHAP, 73%; DHAP, 88%; EPIC, 58%; ICE, 65%; and GV, 76%).[3]

An FDG-avid PET scan was performed for response evaluation. FDG-PET is more accurate than conventional CT

TABLE 1. Stage and Age at Disease Presentation

			Age			
Disease Type	**Early Stage**	**Late Stage**	**< 10 years**	**10-15 years**	**>15 years**	**Total Patients**
Primary progressive disease	3	10	4	2	7	13
Early relapse	1	4	1	3	1	5
Late relapse	2	5	0	4	3	7
Total, No. (%)	6 (24)	19 (76)	5	9	11	25 (100)

TABLE 2. Disease Response Before HDC and at Day 60

Disease at Presentation (No.)	Disease Response Before HDC			Disease Response at Day 60 Scan After HDC	
	CR (68%)	PR (24%)	PD (8%)	CR (88%)	Disease Progression (12%)
Primary progressive disease (13)	10	2	1	11 (84)	2 (16)
Early relapse (5)	2	3	0	5 (100)	—
Late relapse (7)	5	1	1	6 (86)	1 (14)

NOTE. Data are presented as No. or No. (%).
Abbreviations: CR, complete response; HDC, high-dose chemotherapy; PD, progressive disease; PR, partial response.

and is highly predictive in the pretransplantation setting.[16] The prognostic relevance of the metabolic imaging is well established in adults, but has not been studied previously in children.[17-19] However, newer evidence is emerging in the pediatric population whereby response to PET scan is being considered an independent predictive factor.[20] Our analysis is the first from our part of the world in which a PET scan was performed for response evaluation, to our knowledge.

The PET-based response before taking patients for HDC and SCT in PPD was CR in 10 patients (77%) and PR in two patients (15%), and one patient (8%) had progression. In early relapse, CR was achieved in two patients (40%) and PR in three patients (60%), whereas in late relapse, CR was achieved in five patients (71%), PR in one patient (14%), and the disease progressed in one patient (14%). A number of prognostic factors are associated with poor outcomes in patients with relapse or refractory HL. Responses to salvage chemotherapy and disease status at transplantation are also highly predictive of outcome.[7,21] Our analysis shows that 92% (23 patients) had either CR or PR to salvage chemotherapy, and only two patients had PD at the time of transplantation. This is in line with international data suggesting that outcomes are better if the disease is chemotherapy sensitive and does not show progression before the patient undergoes HDC.

BEAM chemotherapy was the conditioning regimen in all patients with the exception of the patient for whom BCNU was replaced by bendamustine because of pulmonary interstitial disease with bleomycin used as the first-line chemotherapy. Common toxicities seen in all patients were neutropenia and grade 2 mucositis.

TABLE 3. Outcomes According to Type of Disease at Last Follow-Up Visit

Disease at Presentation (No.)	Outcomes According to Type of Disease at the Last Follow-Up Visit, No. (%)		
	Remission	Relapse	Death
Primary progressive disease (13)	11 (84)	1 (8)	1 (8)
Early relapse (5)	4 (80)	1 (20)	—
Late relapse (7)	6 (86)	—	1 (14)

All episodes of febrile neutropenia were treated with broad-spectrum antibiotics, and all patients recovered from these episodes. No acute complication caused by chemotherapy was observed, and patients were discharged between day 18 and day 24. Only two patients died as a result of disease progression after HDC chemotherapy. There were no treatment-related deaths in this cohort of patients. There are numerous studies on toxicities seen in patients with HDC chemotherapy, and one European series reported that interstitial pneumonitis, fungal infections, cardiac complications, and veno-occlusive disease were seen.[22] Patients were followed up on an outpatient basis at regular intervals and screening cardiac and pulmonary evaluations were performed; however, as of the last follow-up, no long-term complications had been reported. Disease response was reassessed on day 60 of SCT, and an overall complete response was seen in 88% and relapse or progression in 12% of patients. In our analysis, the two patients who had progression before going for HD progressed further and later died as a result. This supports the theory that chemotherapy resistance and response to PET scan do play an important role in predicting outcomes.

Patients who relapsed after HD are on palliation and were alive at the last follow-up. In terms of their disease, 84% of patients with PPD, 80% with early relapse, and 86% with late relapse were in remission when last seen.

PPD is an adverse factor in OS and EFS. The single ST-HD-86 trial showed three groups with risk stratification. PD while receiving or within 3 months of primary treatment (disease-free survival [DFS], 41%; OS, 51%) had the worst prognosis, early relapse 3 to 12 months from primary treatment had better OS (DFS, 55%; OS, 78%), and late relapse $>$ 12 months from primary treatment had significantly better DFS (DFS, 86%; OS, 90%).[6]

OS in our study was 92% at 4 years, and EFS was 80%, which is better than that reported in other studies. The reason for the better outcomes is likely the small size of patients compared with those in other studies. As mentioned previously in the text, 19 patients with disease progression or early relapse were excluded from this analysis. Hence, we believe that the patients selected for transplantation explain our good outcomes, so there may be selection bias. The ST-HD-86 trial looked at chemotherapy regimens, but their analysis does not mention if

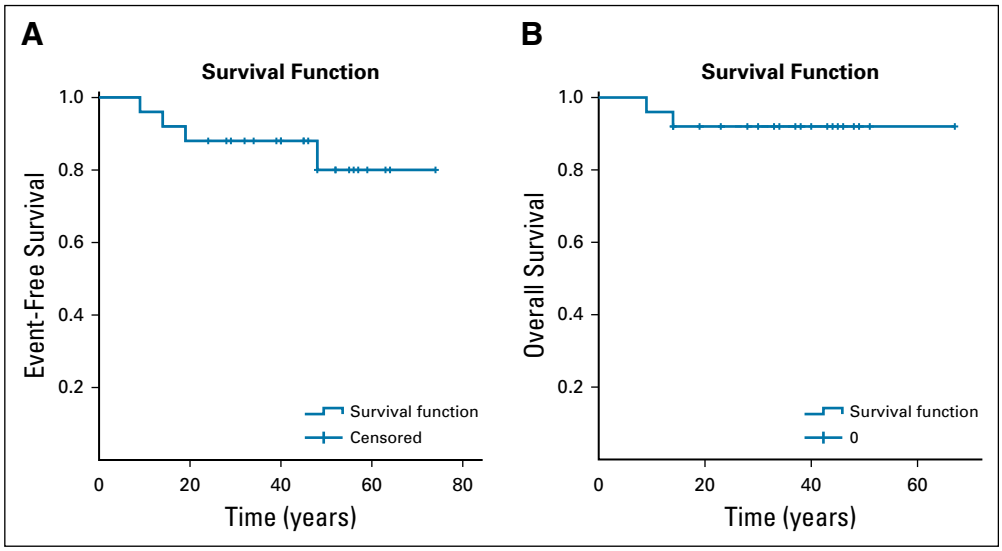

FIG 1. Kaplan-Meier curves at 4 years. (A) EFS (event-free survival). (B) Overall survival.

PET was performed for response assessment; this could be one reason why our results are better even in PPD, because there is evidence predicting better outcomes on the basis of PET scan responses. Giulino-Roth et al[23] have reported a 10-year EFS and OS of 67.1% and 74.1%, respectively. Our survival follow-up for this study was at 4 years as compared with the previously mentioned studies, and that might be another factor causing differences in OS and EFS values.

Allogeneic SCT has been used as a treatment option in advanced HL for young patients without significant comorbidities; however, nonrelapse mortality often exceeded 50% in myeloablative approaches, and relapses were not uncommon. Not enough data are available in children regarding reduced intensity conditioning regimens.

Despite using aggressive chemotherapy regimens and SCT, 10% to 40% of patients continue to have refractory or relapse disease, and newer therapies are required. Recent advances in the understanding of the tumor biology of HL have led to a new era of targeted and immunotherapies with remarkable activity. Most notably, the antibody-drug conjugate brentuximab vedotin and the immune checkpoint blockers pembrolizumab and nivolumab have been approved recently by the US Food and Drug Administration.[24] For developing countries, however, the use of novel therapies is limited because of cost issues.

In conclusion, our retrospective analysis shows good outcomes in patients who had PD, refractory, and relapse disease. Disease response before transplantation is important in predicting outcomes. Minimal treatment-related complications occurred.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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