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JSCTT ISSN 2577-1469 JOURNAL OF STEM CELL THERAPY AND TRANSPLANTATION

Research Article

Fifteen year Follow-up of Relapsed/Refractory Patients with Hodgkin Lymphoma Treated with Autologous Hematopoietic Stem Cell Transplantation

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Submitted: June 24, 2024
Approved: July 01, 2024
Published: July 02, 2024

How to cite this article: Abredabo S, Chiang H, Klein L, Rodriguez T, Bitran JD. Fifteen year Follow-up of Relapsed/Refractory Patients with Hodgkin Lymphoma Treated with Autologous Hematopoietic Stem Cell Transplantation. J Stem Cell Ther Transplant. 2024; 8(1): 033-037.
https://dx.doi.org/10.29328/journal.jsctt.1001040

Abstract

We reviewed our outcomes of patients with relapsed/refractory Hodgkin Lymphoma treated with autologous stem cell transplant over a 30-year period, 1992 to 2022 and are reporting 15-year Disease-Free Survival (DFS) and Overall Survival (OS) of the 36 patients treated (19 men, 17 women, median age 41). Over the years there were different preparative regimens employed (carmustine, etoposide, melphalan and BCNU, etoposide, cytarabine, and melphalan) as well as post-transplant consolidation therapy (brentuximab). With a median follow-up of 15 years, the DFS is 52% and OS is 64%. Long-term complications include cardiomyopathy and second malignancies.

The use of better salvage regimens and post-transplant consolidation therapy should lead to better outcomes.

Introduction

Classical Hodgkin lymphoma is a monoclonal lymphoid neoplasm classified by the presence of Reed-Sternberg cells. It represents approximately 10% of all lymphoma cases diagnosed in the United States and is associated with high cure rates of up to 80% [1]. Despite the incorporation of novel agents in front-line therapy, up to 40% of patients with advanced-stage disease and 10% to 15% with limited-stage disease may relapse and require additional treatment [1]. High-dose chemotherapy with autologous stem cell transplantation (ASCT) is still the standard of care for patients with relapsed Hodgkin's Lymphoma (HL) [2].

Over the 30-year study, many different combinations of treatment regimens were utilized and studied but none demonstrated superiority over the others. However, the most commonly used conditioning regimens are cyclophosphamide, carmustine (BCNU) and etoposide, otherwise known as CBV, or the combination of BCNU, etoposide, cytarabine (Ara-C), and melphalan, also known as BEAM [3]. The addition of checkpoint inhibitors and Brentuximab Vedotin (BV) have been incorporated over the years, assisting in overcoming the relapsed and refractory cases [4]. The cure rate with ASCT is 60% - 70% in relapsed disease and 30% in those with refractory disease, indicating a significant portion of patients are still at risk for relapse or progression after autologous hematopoietic stem cell transplantation. The use of post-transplant maintenance therapy has improved outcomes in this high-risk patient population [5]. The phase 3 AETHERA trial demonstrated that consolidation after transplantation with one year of brentuximab vedotin, a CD30 antibody-drug conjugate, improved progression-free survival [4]. In addition to improving cure rates, it is important to recognize and manage long-term complications of therapy.

While there have been a number of studies that have reported 3-year and 5-year Disease-Free (DFS) and Overall Survival (OS) for patients with relapsed HL treated with ASCT, few studies have reported ten-year DFS and OS. Additionally, we are aware of no reports of 15-year DFS and OS in this patient population. We wish to report 15-year DFS and OS in patients with relapsed or refractory HL treated at a

single institution with a median follow-up of 15 years. As this population continues to survive past the previously reported 10 years, having further data that corroborates the efficacy of evolving therapies to extend survival rates, will be valuable in determining management for these HL patients. It would also be beneficial to understand the long-term complications and explore different possibilities of minimizing them to allow for a better quality of life and decrease mortality.

Methods

We retrospectively reviewed the records of the 36 patients with relapsed Hodgkin's Lymphoma who were treated with high-dose chemotherapy and autologous hematopoietic stem cell transplantation (AHSCT) at Advocate Lutheran General Hospital from 1992 to 2022. Of these 36 patients, there were 19 males and 17 females with a median age of 41 years (range 21-70) and a median performance status of 1 (range 0-1). All 36 patients had to be in sensitive relapse as determined by computerized axial tomography (CT) of the chest, abdomen, and pelvis or by positron emission tomography (PET) scan in order to be considered eligible candidates for AHSCT and met the eligibility criteria of hemoglobin > 10.5 gms/dL, WBC > 3000 cells/microliter, absolute neutrophil count > 1500 k/mcL, platelets >100,000 cells/microliter, serum creatinine normal than 1.5 times normal, normal ALT, AST, bilirubin, alkaline phosphatase, left ventricular ejection fraction of > 50% as measured either by gated heart scan or Echocardiogram, normal pulmonary function tests with a minimum DLCO > 70%. Informed consent was obtained from all 36 patients as per institutional policy and in granting consent, we were allowed to review their records and report results to the CIBMTR to be used in potential publications.

Once patient consent was obtained, all patients underwent placement of either a VasCath™ catheter (Bard, Salt Lake City, Utah) or a Hickman Trifusion™ catheter (Becton Dickinson, Franklin Lakes, NJ). Patients then received filgrastim 10 micrograms/kg for 4 consecutive days typically on a Friday. In 2008, plexiflor was added to filgrastim.

Apheresis and CD34+ collection

Apheresis commenced when the CD34 count as determined by flow cytometry was equal to or greater than 20 cells per microliter. Apheresis was performed at least a 6 L exchange initially on a COBE Spectra and since 2000 on a Spectra Optia. A minimum of $2x10^6$ CD34+ cells/kg were collected and cryopreserved.

Conditioning regimens

The preparative regimens used were carmustine (BCNU), etoposide, and melphalan (CEM) [5] and starting from 2006 to the present BCNU, etoposide, cytarabine, and melphalan (BEAM) [6].

Since 2018, Brentuximab (Br) has been added to BEAM as post-transplant consolidation therapy in 13 patients.

Supportive care

Following the completion of the conditioning regimen and infusion of the CD34+ collection product, all patients received prophylactic antibiotics that started on day -1 that included valganciclovir, oral ciprofloxacin or levofloxacin, and oral fluconazole. Filgrastim 5 micrograms/kg was started on day 0 until 2012 when the protocol was changed to be administered on day +5 and continued until hematologic recovery.

Follow-up and response to AHSCT

Patients were followed up closely following discharge from the hospital, weekly for the first month, then monthly for the first 6 months, and then every 3 months for the first 5 years. After 5 years, patients were seen every 6 months until 10 years. Thereafter, patients were seen for follow-up annually. Response to AHSCT was determined on day +100 by CT of the chest, abdomen, and pelvis or PET-CT.

Disease-free survival and survival

Disease-Free Survival (DFS) and overall survival were measured from day 0 until relapse of death of any cause. Survival and DFS were calculated by Kaplan-Meier plots.

Results

From 1992 to 2023, 36 patients with relapsed Hodgkin's lymphoma were treated with AHSCT. These patients were followed over the course of a 30-year time period with determination of complete, partial, or no response. Of the 36 patients, fifteen (41.7%) were treated with CEM, and 21 (58.3%) were treated with BEAM. In 2018, brentuximab was included in the BEAM regimen as a post-transplant consolidation therapy for 13 (36.1%) of the 21 patients (61.9%). Of the 15 patients treated with CEM, 9 (60%) achieved a Complete Response (CR) and of the 20 patients treated with BEAM, 16 (80%) achieved a CR. The median time to hematologic recovery was 12 days (range 8-21 days). There were a total of 4 patients in our cohort that received maintenance brentuximab, all 4 patients achieved and maintained a CR.

Treatment-related complications, seen in Table 1, included *Staphylococcus epidermidis* sepsis in three patients, two treated with CEM and one treated with BEAM. Three patients developed *Escherichia coli* sepsis, two were treated with CEM, and one was treated with BEAM. One patient treated with CEM developed an esophageal perforation that led to death. Long-term complications of high-dose therapy included cardiomyopathy (6 patients), ischemic heart disease, liposarcoma, breast cancer stage III, and peripheral neuropathy that occurred in one patient each. None of the patients that received brentuximab had any long-term treatment-related complications including neuropathy.

The actual 15-year Disease-Free Survival (DFS) and Overall Survival (OS) are shown in Figures 1,2 and are 55% [CI 48.5%-61.5%] and 61% [54.5%-67.5%] respectively. Each year, the patients that withdrew or a death occurred, DFS and OS were adjusted and survival was determined. Table 2 lists the series that have reported 10-year data in patients with relapsed or refractory HL. As shown in Table 2 and our series there is a cohort of patients with relapsed or refractory HL that are long-term disease-free survivors.

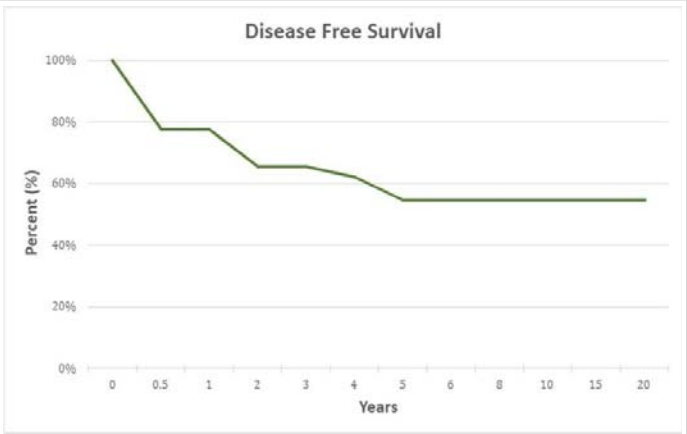

Figure 1: Disease-Free Survival (DFS) was determined over a 15-year time period which takes into account patients who have withdrawn from the study and those who have resulted in death. Beyond 5 years, disease-free survival was found to be 55%.

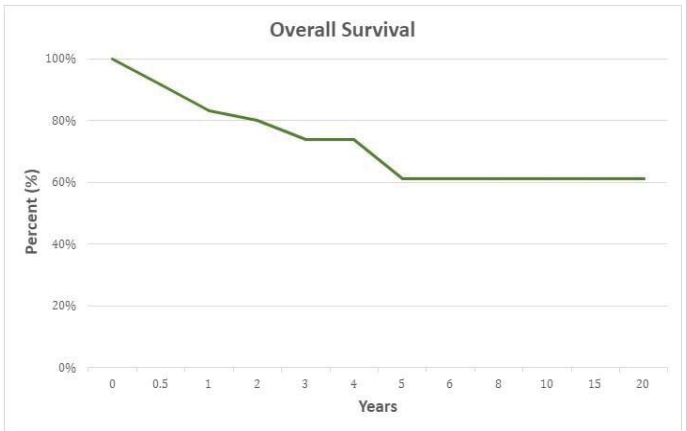

Figure 2: Overall Survival (OS) was determined over a 15-year period which takes into account patients who have withdrawn from the study and those who resulted in death. Beyond 5 years, overall survival was found to be 61%.

Table 1: Treatment and long-term complications between the two treatment regimens, CEM and BEAM.

	CEM	BEAM
Treatment complications		
S. epidermidis sepsis	2	1
E. coli sepsis	2	1
Esophageal perforation	1	0
Long-term complications		
Cardiomyopathy	2	4
Ischemic heart disease	0	2
Liposarcoma	1	0
Breast cancer	1	0
Peripheral neuropathy	0	1

CEM: Carmustine, Etoposide, Melphalan; BEAM: BCNU (carmustine), etoposide, Ara-C (cytarabine), melphalan *S. epidermidis*: *Staphylococcus epidermidis; E. coli*: *Escherichia coli*

Table 2: Long-term, 10-year Disease Free (DFS) and Overall Survival (S) in Hodgkin's Lymphoma.

Author	Year	No of pts	Median Follow-up	10 yr DFS	10 yr S
Lavoie, et al.	2004	100	11.4 years	54%	54%
Majhail, et al.	2006	141	6.3 years	45%	47%
Sirohi, et al.	2008	195	10.3 years	37%	49%
Current series	2023	35	13 years	55%	61%

Discussion

The results reported herein are similar to outcomes previously reported [7-9] with the exception being that we are reporting 15-year DFS and OS as opposed to 10-year survival (Table 2). Our outcome of a 15-year DFS of 54% is encouraging and is in line with that seen with prior 10-year data reported. The value of having longer follow-up is evaluating the long-term complications of therapy. Survivorship is key as over 50% of patients with Hodgkins' Lymphoma even in the relapse setting will be cured.

The long-term complications that our cohort of patients experienced included ischemic heart disease, cardiomyopathy, breast cancer, and liposarcoma. Whether these long-term effects are a consequence of high-dose chemotherapy is not entirely clear. There were no unforeseen adverse effects with longer follow-ups as seen with our patient population when compared to previous 10-year outcomes reported [7-9]. Interestingly, we have not observed secondary treatment-related leukemia or myelodysplasia even with longer-term follow-up.

The limitation of this study is that this retrospective study includes a small patient cohort. As shown with the prior 10-year retrospective studies, the patient cohorts were over 100 compared to our patient population of 36. An additional limitation is the small number of patients who received maintenance brentuximab. The FDA approval for maintenance brentuximab based on the AETHERA trial was in March of 2018. Most of our patients were treated prior to this. This is important as maintenance strategies are now being incorporated to further improve outcomes.

There are many strategies that are being explored to improve outcomes further. One strategy reported by Herrerra, et al. [11] involves using nivolumab at a dose of 3 mg/kg every 3 weeks as initial salvage therapy and employing PET scans after cycles 3 and 6 to determine if additional chemotherapy with Ifosfamide, Carboplatin, and Etoposide (ICE) is necessary. Of the 37 patients enrolled and evaluable for response, 33 of 37 (89%) achieved a complete (CR) or partial response and the CR rate was 59% (22/37). Of the 27 patients who proceeded to autologous stem cell transplantation, the 1-year DFS was 79.

An alternate strategy is examining the potential role of nivolumab post-Autologous Stem Cell Transplantation (ASCT) as a "consolidative therapy". Herrera, et al. reported the results of a phase II study [12] that explored the use of

nivolumab 3 mg/kg added to brentuximab 1.8 mg/kg given every 21 days for 8 cycles (24 weeks). They enrolled 59 patients with high-risk HL in this trial. The median time to start the combination was 54 days (range 30-75 days). The most frequent adverse effects were peripheral neuropathy, neutropenia, diarrhea, nausea, and arthralgias. The actuarial DFS at 1 year is 95%. Bacher, et al. reported the results of a phase II trial of nivolumab alone, 240 mg IV every 14 days, used as "consolidative therapy" post-ASCT in high-risk HL for 6 months. They enrolled 37 patients and the most common adverse effects were diarrhea, fatigue, bone pain, a decrease in the neutrophil count, pruritus rash and vomiting. The reported DFS at 6 months was 92% the use of these novel therapies with autologous stem cell transplant can result in better overall outcomes for patients with relapsed or refractory HL treated with ASCT [13-22].

Conclusion

Relapsed or refractory Hodgkin lymphomas have been treated with different conditioning regimens after autologous stem cell transplant over the years and have been previously documented as a 10-year follow-up. With evolving therapies, including the incorporation of novel agents such as brentuximab, our 15-year follow-up that demonstrates a 54% disease-free survival is encouraging. As further data results, we will tailor the treatments and determine how to better manage or prevent the long-term complications possibly associated with them to improve outcomes in the future.

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