

# Analysis of Relapsed/Refractory Hodgkin Lymphoma Treated with Autologous Transplantation: A Single-Center Experience

## Abstract

**Introduction:** Hodgkin lymphoma (HL) is one of the common lymphomas with high cure rate. **Aims:** The aim was to study the outcome of relapsed/refractory HL treated with autologous transplantation. **Objectives:** The objective was to study the overall survival, overall response, and disease-free survival of the relapsed/refractory HL after autologous transplantation. **Methods:** It was a retrospective study conducted over a period of 8 years in our center using computer-based database and medical records as the data source. **Results:** A total of 22 patients were diagnosed with relapsed/refractory HL of which majority of cases were male patients (59%) with a mean age of 29 years (range: 15–57 years) and were Stage 4A (40.9%), with nodular sclerosis (54.5%). The overall response rate was 81.8% with 9.1% complete response, 72.7% partial response, and 4.5% stable disease; the overall survival was  $77.92 \pm 6.65$  months, and disease-free survival was  $69.66 \pm 8.13$  months. **Conclusion:** Autologous stem cell transplant plays an integral role in the treatment of patients with relapsed/refractory Hodgkin lymphoma.

**Keywords:** Autologous, Hodgkin, refractory, relapsed

## Introduction

Hodgkin lymphoma (HL) is a type of malignancy with high cure rates. However, about 15% of patients with early-stage disease and about 20%–30% with advanced-stage disease either have refractory disease or tend to have relapse of the disease after initial therapy.<sup>[1]</sup> Approximately 80% of patients have symptoms or signs of the disease at relapse.<sup>[2]</sup> The goal of the treatment in relapsed/refractory HL is long-term disease control while minimizing the toxicity and complications of therapy. High-dose chemotherapy followed by autologous stem cell transplant (ASCT) is the treatment of choice for relapsed/refractory disease.<sup>[3,4]</sup> Although ASCT has not shown to improve the overall survival, it is considered the standard of care.

## Methods

This was a retrospective study conducted from January 2010 to July 2018 in the department of hematology at our 200-bedded tertiary cancer hospital. The

study was initiated using computer-based database and medical records as the data source. Relapsed/refractory HL cases were defined as clinically symptomatic or progressive or PET-CT scan relapsed/progressive patients with or without proven histopathology. Relapse case was defined as a case that came back after the remission from first-line chemotherapy. The refractory case was defined as a case that progressed during the treatment with first-line chemotherapy.

A study pro forma was established, which included patient identification, diagnosis, staging, histological types, international prognostic index score, chemotherapy types and number of cycles, date of relapse, conditioning regimen, and date of transplant. Patient's disease status till the last follow-up was recorded along with the date of relapse and/or death. After the collection of reports, statistical analysis was conducted using SPSS Software version 20. The primary objective of our study was to calculate the overall survival post autologous transplant, while the secondary objectives were to calculate the overall response and disease-free survival in our patients. Survival curves were plotted with

**Vishal Kulkarni,  
Sulav Sapkota,  
Girish V Badarkhe,  
BJ Srinivas,  
Radheshyam Naik**

*Department of Hematology  
and Medical Oncology, HCG  
Enterprises Ltd., Bengaluru,  
Karnataka, India*

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### Address for correspondence:

*Dr. Sulav Sapkota,  
HCG Enterprises Ltd,  
Bengaluru, Karnataka, India.  
E-mail: dr.sulavsapkota@yahoo.  
com*

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Kaplan–Meier methodology. Patients who were lost to follow-up after therapy were censored as alive at their last follow-up. Descriptive statistics was used for the analysis of demographic variables, disease characteristics, and response rates.

## Results

### Patients characteristics

A total of 22 patients were diagnosed with relapsed/refractory HL during the study period. In our study, majority of the cases were male patients (59%) with a mean age of 29 years (range 15–57 years) and were Stage 4A (40.9%), with nodular sclerosis (54.5%) and International Prognostic Score (IPS) score of two (40.9%). B symptoms at diagnosis were recorded in 45% of the patients. None of the patients were diagnosed with tuberculosis prior to the histological diagnosis of HL – one of the differential diagnoses in these patients. Nine percent of the patients had comorbidities. All (100%) of the patients had the Eastern Cooperative Oncology Group performance status (ECOG-PS) of  $\leq 2$ . None of the patients had acquired immunodeficiency syndrome at the time of diagnosis, and no patients had a history of exposure to radiation before the diagnosis [Table 1].

### Lymphoma characteristics

Stage 4A was the most common presentation with 40.9%. The most common histopathology was nodular sclerosis observed in 54.5%, followed by mixed cellularity, lymphocyte-predominant type, and lymphocyte-depleted type, in 36.5%, 4.5%, and 4.5%, respectively. IPS could be estimated in all the patients. IPS score  $\leq 4$  was observed in 95.5% (21/22) of the patients. No bone marrow involvement and extranodal sites of disease was observed. Bulky disease (defined as largest tumor size  $\geq 10$  cm) was also not observed in our patients. There were 9 relapsed cases and 13 refractory cases in total [Table 2].

### Treatment characteristics

Most of the patients ( $n = 21$  patients, 95.5%) were treated with standard ABVD chemoregimen before the relapse, while 4.5% of the patients received CHOP regimen due to advanced age or comorbidities. Six cycles of chemotherapy were completed by all of the patients. Radiation was given to 22.5% of the patients for either bulky sites or residual disease at the end of chemotherapy. Post relapsed/refractory, the most common second-line regimen used was ifosfamide, carboplatin, and etoposide (ICE) regimen (55%), followed by dexamethasone, high-dose Ara-C, and Cisplatin (DHAP); gemcitabine, dexamethasone, and cisplatin; and mesna, ifosfamide, mitoxantrone, and etoposide regimens. Majority of the patients after the second-line chemotherapy had partial response (PR) (73%) before undergoing

**Table 1: Clinical characteristics of patients**

Patients characteristics	n (%)
Mean age	29.6 $\pm$ 12
Male	13 (59.1)
Female	9 (40.9)
Age group	
15–30	16 (73)
30–45	3 (13.5)
45–60	3 (13.5)
>60	0
National patients	17 (77.5)
International patients	5 (22.5)
Professional	11 (50)
Students	7 (32)
Homemaker	4 (18)
Comorbidity	2 (9)
TB	0
Retropositivity	0
Radiation exposure before	0
ECOG 1	22 (100)

TB – Tuberculosis; ECOG – Eastern Cooperative Oncology Group

**Table 2: Clinical characteristics of lymphoma**

Lymphoma characteristics	n (%)
Staging	
IA	1 (4.5)
IB	1 (4.5)
IIB	3 (13.6)
IIIA	2 (9.1)
IIIB	3 (13.6)
IVA	9 (40.9)
IVB	3 (13.6)
Histological types	
Lymphocyte depleted	1 (4.5)
Mixed cellularity	8 (36.5)
Nodular lymphocyte predominant HL	1 (4.5)
Nodular sclerosis	12 (54.5)
IPS score	
1	8 (36.4)
2	9 (40.9)
3	4 (18.2)
4	0
5	1 (4.5)
B symptoms	10 (45)
Relapsed cases	9 (41.5)
Refractory cases	13 (58.5)

HL – Hodgkin lymphoma; IPS – International prognostic score

autologous transplantation. Post autologous transplant, four patients had relapsed, of which two patients received the third-line six cycles of Gemox chemotherapy, while one patient received radiation to the relapsed mediastinum. About 40.5% of the patients developed an infection during the transplant, which was salvageable with broad-spectrum antibiotics. Transplant-related mortality was zero during our transplantation [Table 3].

### Transplantation characteristics

All the relapsed/refractory patients underwent autologous transplantation at our center. The conditioning regimen used

**Table 3: Treatment characteristics**

Treatment characteristics	n (%)
1 <sup>st</sup> line chemotherapy	
ABVD regimen	21 (95.5)
CHOP regimen	1 (4.5)
Second-line chemotherapy (salvage)	
ICE regimen	12 (55)
DHAP regimen	6 (27)
GDP regimen	2 (9.0)
MINE regimen	1 (4.5)
ABVD regimen rechallenge	1 (4.5)
Response after salvage chemo	
CR	2 (9)
PR	16 (73)
SD	1 (4.5)
PD	3 (13.5)
Third-line chemo posttransplant	2 (9)
GEMOX regimen	
Radiation before transplant	5 (22.5)
Radiation after transplant	1 (4.5)

ICE – Ifosfamide, carboplatin, and etoposide; DHAP – Dexamethasone, high-dose Ara-C, and cisplatin; CR – Complete response; PR – Partial response; SD – Stable disease; PD – Progressive disease; ABVD – Adriamycin, bleomycin, vinblastine, dacarbazine; CHOP – Cyclophosphamide, doxorubicin, oncovin, prednisone; GEMOX – Gemcitabine, oxaliplatin; MINE – Mesna, ifosfamide, mitoxantrone, and etoposide

**Table 4: Transplantation characteristics**

Transplant characteristics	n (%)
Autologous transplant cases	22 (100)
Conditioning regimen BEAM	22 (100)
Mean stem cells collected ( $\times 10^6/\text{kg}$ )	$6.022 \pm 3.4$
Mean engraftment day	$13.3 \pm 3.8$
Infections during transplant	9 (40.5)
Response rate	
Overall response rate	81.8%
CR	2 (9.1)
PR	16 (72.7)
SD	1 (4.5)
PD	3 (13.7)
Overall death	2 (9.0)
Transplant related death (TRM)	0
Death due to AML transformation	1 (4.5)
Death due to relapse	1 (4.5)
Relapse/refractory cases	4 (18)
Overall survival (months)	$77.92 \pm 6.65$
Disease free survival (months)	$69.66 \pm 8.13$
Lost to follow-up cases	6 (27)

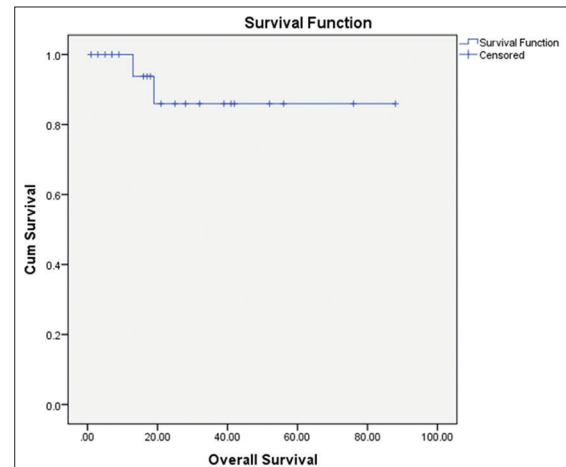
TRM – Transplant related mortality; CR – Complete response; PR – Partial response; SD – Stable disease; PD – Progressive disease; BEAM – BCNU, etoposide, cytarabine, melphalan

was BEAM regimen (100%) to treat patients for autologous transplantation. The mean stem cell collection during the stem cell transplantation was  $6.022 \pm 3.4 \times 10^6/\text{kg}$  and the mean neutrophil engraftment duration was  $13.3 \pm 3.8$  days. The overall response rate was 81.8% with 9.1% complete response (CR), 72.7% PR, and 4.5% stable disease. The overall survival was  $77.92 \pm 6.65$  months and disease-free survival was  $69.66 \pm 8.13$  months as shown in Figures 1 and 2, respectively. There were two deaths (9.0%) during the follow-up period, one with the relapse and other with acute myeloid leukemia transformation. A total of four re-relapses occurred after autologous transplantation, and six (27%) patients were lost to follow-up [Table 4].

### Discussion

This report comprises about 96-month follow-up of a single institution cohort of patients with refractory/relapsed HL who underwent ASCT. The results showed that high-dose chemotherapy followed by ASCT can induce disease control and improve the prognosis of patients with advanced refractory or relapsed HL. The patient population of this study was heterogeneous and pretreated, with a median of two lines of chemotherapy regimens before transplantation. Despite this, 91% of the patients were alive and 86.5% disease-free at the end of the follow-up.

The diagnosis of relapsed or refractory HL is mostly done clinically as most patients are symptomatic at presentation. Occasionally, however, new lesions or lesions at the initial site are picked up on imaging studies. NCCN v1.2017 recommends obtaining contrast computed tomography (CT) scan of the neck, thorax, abdomen, and pelvis at 6, 12, and 24 months after completion of the therapy or as clinically indicated. The role of positron-emission tomography (PET)-CT scan in the diagnosis of relapsed or refractory disease is still not clearly defined. NCCN v1.2017 recommends PET-CT only if the last PET was Deauville 4–5 to confirm CR. Although these imaging modalities expose the patient to various



**Figure 1: Overall survival postautologous transplantation**

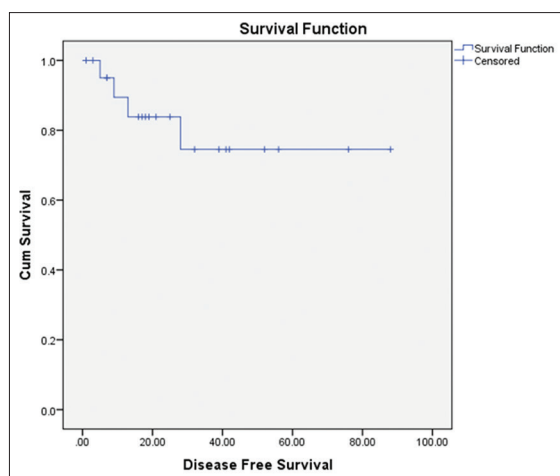


Figure 2: Disease free survival post autologous transplantation

risks, the benefits over clinical detection are not very clear.<sup>[5,6]</sup> Repeat biopsies of the persistent or new lesions are recommended. Repeat biopsies are especially useful in patients with refractory disease and late relapses (3–5 years after primary treatment) or treating physician suspects another malignancy. In our study, clinical examination and PET-CT scan with or without biopsy had been used to confirm the relapsed/refractory cases.

Several prognostic factors have been evaluated by various investigators to predict survival in relapsed/refractory disease.<sup>[7-12]</sup> These include patient-related factors such as poor PS, age >50 years, the presence of B symptoms, poor response to the first chemotherapy, low albumin, anemia, and lymphocytopenia. Disease-related factors include Stage III/IV at presentation, extranodal disease, relapse in the previous radiation field, residual disease pretransplant, and time to relapse <1 year. In our study, advanced stage had been found to be associated more with relapsed/refractory cases, while IPS score was not found to be associated.

Several studies have emphasized the need for cytoreduction prior to transplant. Hence, various salvage chemotherapy regimens have been studied in randomized controlled trials.<sup>[9,13-22]</sup> However, there is no gold standard salvage chemotherapy, as head-to-head comparison among these various regimens has not been conducted. Several regimens such as gemcitabine, vinorelbine, and pegylated liposomal doxorubicin; ifosfamide, gemcitabine, and vinorelbine; and gemcitabine, carboplatin, and dexamethasone have also been tried with good results.<sup>[23-25]</sup> However, these regimens have not been tried in randomized controlled trials. The decision to use the appropriate regimen is usually made by the treating physician according to the institutional experience and protocols and individual patient-related factors. One of the major factors which decide on the choice of salvage chemotherapy regimens is the impact on subsequent peripheral blood stem cell (PBSC) mobilization. Regimens containing melphalan have been reported to impair PBSC mobilization.<sup>[26,27]</sup> Hence, regimens which do

not contain melphalan like ICE and DHAP have become popular in recent years. One study concluded that although both ICE regimen and DHAP regimens were safe, the former had slightly more response rates.<sup>[28]</sup> Bendamustine, lenalidomide, and everolimus have also been tried in several Phase 2 trials. We have used ICE regimen in majority of cases and we have found the maximum benefits with minimum side effects.

Newer class of agents have also been used in Phase 2 trials. Notable among these are the antibody–drug conjugates and programmed death receptor-1 (PD-1) inhibitors (immunotherapy). Brentuximab vedotin (anti-CD30 antibody–drug conjugate) was initially used as single agent. Recently, there has been an attempt to combine this agent with conventional salvage chemotherapy regimens with good success rates.<sup>[29-35]</sup> Nivolumab (PD-1 inhibitor) has also been used recently. A Phase 1/2 trial demonstrated good efficacy and safety when combined with brentuximab.<sup>[36]</sup> Further larger Phase 3 studies are required to validate the results of these preliminary studies involving newer agents. BEAM regimen is most commonly used as high-dose conditioning chemotherapy before ASCT. A trial by GHSG reported higher freedom from treatment failure in patients who underwent ASCT following HDC compared to HDC alone. The overall survival however remained the same.<sup>[37]</sup> Hence, NCCN v12017 recommends HDC followed by ASCT for all patients with relapsed/refractory HL.

Survival after relapse post-ASCT remains poor. It is estimated that up to 50% of patients ultimately relapse following ASCT. Treatment of such patients is particularly challenging. RIC allogeneic SCT remains one of the options but is limited by various factors such as donor availability, patient preference, and lack of sensitivity of the disease to chemotherapy. In our study, a total of four cases relapsed and one patient developed acute myeloid leukemia post autologous transplantation. Of four patients, one died, two received third-line GEMOX chemotherapy, and fourth received radiation to the mediastinum. Later, three patients were doing well till the last follow-up.

Brentuximab vedotin has been successfully used in such patients. The 5-year survival rates are encouraging considering the heavily pretreated nature of these individuals. It can be used even if treated previously in the same patient.<sup>[38-40]</sup> Nivolumab and pembrolizumab have also been used in relapse post-ASCT with good results.<sup>[41-43]</sup> Very recently, a combination of immunotherapy and brentuximab was administered in a small group of patients who had relapsed post-ASCT. The overall response rates were 100%. No serious Grade 3/4 toxicities which would lead to treatment discontinuation were observed.<sup>[44]</sup> Lenalidomide alone or in combination with bendamustine has been tried. Other agents which have given mixed results are histone deacetylase inhibitors such as panobinostat and mTOR



inhibitor everolimus.<sup>[45-47]</sup> However, we did not use any of these newer treatments in our re-relapsed cases.

The strength of this study lies in the fact that this is one of the considerable number of patients' data from India on relapsed/refractory HL treated with autologous transplantation. However, this is a retrospective analysis which has its inherent flaws of missing data and lack of follow-up.

## Conclusion

ASCT plays an integral role in the treatment of patients with HL. Most patients with HL are cured with combination chemotherapy with or without radiation therapy. ASCT is currently the optimal treatment for patients who fail chemotherapy and radiation therapy. Treatment of relapsed HL post autologous transplantation is particularly challenging.

## Consent

Informed consent was obtained from all patients for being included in the study.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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