

## Maintenance therapy with Everolimus in patients with refractory or relapsing Hodgkin lymphoma after autologous stem cell transplantation

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### Abstract

**Introduction:** Patients with relapsing or primary refractory Hodgkin lymphoma, still have unsatisfactory outcomes after high dose chemotherapy followed by autologous stem cell transplantation (ASCT). Brentuximab Vedotin (BV) is the only approved agent for maintenance therapy for up to one year in these patients, however, this agent is often not available or affordable for many patients, especially in the developing countries. In this study, we used Everolimus as maintenance therapy after ASCT among patients with relapsing/refractory Hodgkin lymphoma.

**Materials and Methods:** We collected the data of 20 patients with primary refractory or relapsing Hodgkin lymphoma who had undergone ASCT between June 2016 and June 2021. Everolimus was started at 10 mg daily on day +90 after ASCT for at least two years in patients with stable disease status, confirmed by imaging modalities. Patients were followed for disease status and drug side effects every 3 months.

**Results:** In our single-arm case-series study, the median duration of treatment was 22.95 months. Except for three patients, who had progression, others had no progression and are still receiving Everolimus (85%). No serious side effect was seen. We had no mortality due to disease recurrence.

**Conclusion:** Until now, results showed promising effects of Everolimus in patients with relapsing or primary refractory Hodgkin lymphoma as maintenance therapy after ASCT.

**Key words** Hodgkin lymphoma, relapsing, primary refractory, everolimus, autologous stem cell transplantation

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### Introduction

Hodgkin lymphoma accounts for 10% of all lymphomas<sup>1</sup>. Despite the progress and advancements in treatment of Hodgkin lymphoma, which has led to approximate cure rate of 90%, there remains 10-15% of patients with early-stage and 15-20% of patients with advanced-stage who are at high risks of relapse. In addition, about 15% of patients do not respond to several lines of chemotherapy which is called primary refractory Hodgkin lymphoma<sup>2</sup>. Hematopoietic stem cell transplantation (HSCT) is recommended for primary Hodgkin lymphoma patients in complete response 2

(CR<sub>2</sub>), Partial response (PR1), and beyond. There are some patients with poor risk factors, including primary refractory disease, patients who are not in CR before ASCT, patients who had received more than one salvage chemotherapy, patients with positive positron emission tomography (PET) scan before HSCT and those who relapsed less than 12 months after the end of chemotherapy<sup>3</sup>. Brentuximab Vedotin is recommended after ASCT at the dose of 1.8 mg/kg every three weeks for up to sixteen cycles (one year) for these high-risk patients. Brentuximab Vedotin therapy results in increasing disease-free survival (DFS) but not overall survival (OS)<sup>4</sup>. Meanwhile, some other agents such as

pembrolizumab 200 mg (every three weeks for eight cycles) are being studied and the progression free survival (PFS) and OS were calculated 78% and 100% respectively<sup>5</sup>.

Treatment with Brentuximab Vedotin for up to one-year results in high costs of health-care, especially in developing countries. Also, this drug may not always be available. Everolimus belongs to a class of kinase inhibitors that targets Mammalian Target of Rapamycin (mTOR). This protein kinase, regulates cell growth, metabolism and survival. It is also involved in many critical regulatory cell cycle functions, such as controlling the cellular response to DNA damage and hence, apoptosis<sup>6</sup>. The catalytic domain of mTOR is highly homologous to the lipid domain of phosphatidylinositol 3-kinase (PI3K)<sup>7</sup>. There are growing evidence about the role of PI3K/Akt/mTOR axis in the proliferation, and angiogenesis of lymphoproliferative disorders. Using mTOR inhibitors as a possible therapeutic regimen for controlling the progression of lymphoproliferative malignancies has been a main scientific focus in certain translational and clinical studies<sup>8-11</sup>. Everolimus has been suggested effective in treatment of several subtypes of non-Hodgkin lymphomas and HL, but there has been little data on its efficacy as a maintenance therapy for those of HL patients that undergo hematopoietic stem cell transplantation.

In this study, we evaluated the efficacy of Everolimus as maintenance therapy in patients with high-risk Hodgkin lymphoma who underwent autologous hematopoietic stem cell transplant (ASCT).

## Materials and Methods

### Ethical statement

This study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (SBMU) with the approval code of IR.SBMU.RETECH.REC.1400.185. This study was conducted based on the declaration of Helsinki. The institutional review board committee approved this study. All the patients were informed about the study method and Everolimus, and all their questions regarding this study were addressed before inclusion. Written informed consent was obtained from each of the participant.

### Study design

The inclusion criteria for considering Everolimus as post-transplantation maintenance therapy were: Patients aged 18 years old or above, with primary refractory or relapsing Hodgkin lymphoma (As mentioned in the definition section). All patients had ECOG performance status (PS) 0 and 1, glomerular filtration rate (GFR) of more than 30 mL/min/1.73 m<sup>2</sup>, ejection fraction (EF) of

more than 50% in the transthoracic echocardiography (TTE), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than 3 times upper normal. All patients were first advised to receive standard post-transplantation treatment (Brentuximab Vedotin); those of patients were included only, who were unable to afford standard treatment (Brentuximab Vedotin). Stem cell mobilization and harvesting were done for all patients with standard ward protocols, followed by conditioning regimens. The protocol of conditioning regimen in autologous transplantation in Hodgkin lymphoma in our center is LEAM protocol (Lomustine + Etoposide + Cytarabine + Melphalan). In certain cases, Bendamustine, an alkylating agent, was chosen as a substitute for Lomustine (BeEAM regimen). Lomustine 200 mg/m<sup>2</sup> on day -5, etoposide 300 mg/m<sup>2</sup>/once daily on days -4 and -3, cytarabine 300 mg/m<sup>2</sup>/twice daily on days -4 and -3, melphalan 140 mg/m<sup>2</sup> on day -1 were administered. In patients who received Bendamustine, it was administered at the dose of 200 mg/m<sup>2</sup> on days -5 and -4. Mobilization was performed using Filgrastim only based on the routine protocol of our Bone Marrow Transplantation (BMT) ward. Three months after successful transplantation, patients were evaluated by an imaging modality (Computed tomography (CT-Scan) or Positron emission tomography (PET-Scan)) for evaluating the patient status. In patients with no progression after ASCT, Everolimus (Novartis<sup>®</sup>) was administered at the dose of 10 mg once daily. The reduced to 5 mg once daily in patients who could not tolerate the drug because of side effects<sup>12</sup>. Everolimus was administered for a minimum of 24 months.

For each patient, demographic and laboratory data were obtained. Demographic data included patient age, gender, stage of Hodgkin lymphoma at presentation, evaluation at the end of treatment, chemotherapeutic agents and targeted therapies, stage at relapse in patients with relapsing Hodgkin lymphoma, day of neutrophil engraftment, type of conditioning regimen, and infection history in BMT ward. Laboratory data included mononuclear cells (MNCs) and CD34+ counts in stem cell analysis. Patients were visited monthly in the first three months after transplantation, then every three months thereafter. Patients were assessed for disease status and drug side effects on each of the visits.

### Definitions

Primary refractory patients in Hodgkin lymphoma in our study were patients who had received multi-agent chemotherapy and may also had received targeted therapy such as Brentuximab Vedotin (BV) before the conditioning regimen. Patients must have had the status of stable disease or partial response or complete response. Patients with relapsing Hodgkin lymphoma are charac-

**Table 1. Characteristic data of patients before transplantation**

Patient number	Age/Sex	Initial stage	Primary evaluation of the end of chemotherapy	Primary Refractory (PR) or Relapsing (R)	Chemotherapeutic and targeted therapy agents before transplant	Final evaluation
1	20/M	IV/A	PR	PR	ABVD/GVD/Brentuximab	PR
2	18/M	III/B	PR	PR	ABVD/GVD	PR
3	24/F	III/B	CR	R (with III/B)	ABVD/at relapse ICE with Brentuximab and then GVD	PR
4	34/F	III/B	CR	R (with III/B)	ABVD/at relapse GVD	PR
5	31/M	IV/B	PR	PR	ABVD/ICE	PR
6	43/F	III/A	CR	R (with III/A)	ABVD/at relapse ESHAP then GVD with Brentuximab	CR
7	28/F	III/B	CR	R (with III/B)	ABVD/at relapse GVD	PR
8	32/M	IV/B	PR	PR	ABVD/ICE	PR
9	34/M	II/A	CR	R (with stage II/A)	ABVD/at relapse ICE then GVD with Bendamustine	PR
10	22/M	II/B	PD	PR	ABVD/ICE/GVD	PR
11	23/M	IV/B	PR	PR	ABVD/ICE	PR
12	38/M	IV/B	CR	R (with IV/B)	ABVD/at relapse ICE	PR
13	34/F	II/B	CR	R (with III/A)	ABVD/at relapse ICE	PR
14	20/F	III/B	PD	PR	ABVD/ICE	PR
15	24/F	III/B	CR	R (with III/B)	ABVD/at relapse ICE then GVD then DHAP <sup>8</sup> with Brentuximab	PR
16	19/M	II/A	CR	R (with III/B)	ABVD/at relapse ICE then Brentuximab then GVD	CR
17	32/M	II/B	SD	PR	ABVD/ICE/Bendamustine/RT <sup>10</sup>	PR
18	33/F	II/B	PR	PR	ABVD/ICE	PR
19	25/F	II/B	CR	R (with III/B)	ABVD/at relapse ESHAP then GDP <sup>11</sup>	CR
20	47/F	III/B	PR	PR	ABVD/ICE	PR

ABVD: Doxorubicin (25 mg/m<sup>2</sup>/D1, D15) + Bleomycin (10 mg/m<sup>2</sup>/D1, D15) +Vinblastine (6 mg/m<sup>2</sup>/D1, D15) + Dacarbazine (375 mg/m<sup>2</sup>/D1, D15)  
 GVD: Gemcitabine (1,000 mg/m<sup>2</sup>/D1, D8) + Vinorelbine (20 mg/m<sup>2</sup>/D1, D8) + Liposomal Doxorubicin (15 mg/m<sup>2</sup>/D1, D8)  
 ICE: Ifosfamide (5 g/m<sup>2</sup>/D22) + Carboplatin (5 AUC/D2) + Etoposide (100 mg/m<sup>2</sup>/D1-D3)  
 ESHAS: Etoposide (50 mg/m<sup>2</sup>/D1-D3) + Methylprednisolone (250-500 mg/D1-D4) + Cytarabine (2 g/m<sup>2</sup>/D5) +Cisplatin (25 mg/m<sup>2</sup>/D1-D4)  
 DHAP: Dexamethasone (40 mg/D1-D4) + Cytarabine (2 g/m<sup>2</sup>/twice daily/D2) + Cisplatin (100 mg/m<sup>2</sup>/D1)  
 GDP: Gemcitabine (1,000 mg/m<sup>2</sup>/D1, D8) + Dexamethasone (40 mg/D1-D4) + Cisplatin (75 mg/m<sup>2</sup>/D1)  
 PR, Partial Response; CR, Complete Response; PD, Progressive Disease; SD, Stable Disease; RT, Radiotherapy

terized as patients who had reached complete response but then relapsed. Complete response (CR) was defined as the disappearance of all lymphoma-related abnormality; partial response (PR) was defined as more than 50% reduction in size of lymph nodes. Stable disease (SD) was defined as no change in the imaging data, and progressive disease (PD) was defined as appearance of a new lesion or increasing in the size of previous lesions by 25% or more.

**Results**

Data from 20 patients with high-risk Hodgkin lymphoma who had undergone autologous bone marrow transplantation between June 2016 and June 2021, were collected in this case series study. Based on the previously approved studies, these patients needed maintenance therapy to prevent relapse. 10 males and 10 females were enrolled in this study. Median age was

29.05 years (18-47 years old). Demographic data, disease status before and after transplant, and the type of chemotherapies before transplant are demonstrated in **Table 1**. Thirteen patients had advanced-stage Hodgkin lymphoma before transplant (stage III and IV), of whom, 5 patients had stage IV and 8 patients had stage III disease. Seven patients had early-stage Hodgkin lymphoma (stage I and II). Five patients had B symptoms as an unfavorable risk factor for early-stage disease. Two patients had mediastinal mass larger than 10 cm (patients no 13, 17) as another unfavorable risk factor for early-stage disease. As shown in **Table 1**, patients had received multi-agent chemotherapy. Ten patients had primary refractory disease, in which, they received further salvage treatments (as shown in **Table 1**) and at the end of treatment before transplantation, they had a partial response to the treatment. Ten patients had relapsing Hodgkin lymphoma. At relapse, they received salvage chemotherapy, and at the end of the treatment

**Table 2. Characteristic data of HSCT**

Patient number	Conditioning regimen	Day of engraftment	MNC $\times 10^6$ /kg	CD34 $\times 10^6$ /kg	BMT ward admission complication
1	LEAM	+11	5.8	2.3	None
2	LEAM	+12	5.2	2.2	Febrile Neutropenia
3	BeEAM	+10	10.6	2.5	None
4	BeEAM	+9	4.2	1.9	None
5	LEAM	+12	11.4	3.1	None
6	BeEAM	+10	4.9	1.9	Febrile Neutropenia
7	LEAM	+9	8.5	10.0	None
8	LEAM	+11	5.5	2.0	None
9	LEAM	+12	7.3	1.1	None
10	LEAM	+10	3.4	1.1	Febrile Neutropenia
11	BeEAM	+13	5.6	6.9	None
12	LEAM	+11	6.9	10.7	None
13	BeEAM	+11	8.5	2.6	None
14	LEAM	+9	7.9	6.4	None
15	BeEAM	+13	9.7	3.1	Febrile Neutropenia
16	LEAM	+10	8.3	2.8	None
17	BeEAM	+9	4.2	2.2	Febrile Neutropenia
18	LEAM	+9	5.3	3.8	None
19	LEAM	+11	7.1	2.1	None
20	LEAM	+7	4.7	1.9	None

MNC, Mononuclear cells; LEAM, Lomustine Etoposide Cytarabine Melphalan; BeEam, Bendamustine Etoposide Cytarabine Melphalan; BMT, Bone Marrow Transplantation

before transplantation, seven and three patients had a partial response and complete response to the treatment, respectively. Five of our patients had received Brentuximab Vedotin as a targeted agent without favorable response before autologous hematopoietic transplantation.

Thirteen and seven patients had received LEAM and BeEAM as conditioning regimen respectively. The median day of engraftment was 10.4 days for neutrophil engraftment. The median MNC count was 6.75 cells  $\times 10^6$  per kilogram of body. The median CD34+ count was 3.53 cells  $\times 10^6$  per kilogram of body. We had not any mortality at the time of admission. Five patients developed febrile neutropenia at the day of (+6, +6, +8, +4, +5 for patient's number 2, 6, 10, 15, 17 respectively). Two patients (patient no. 2 and 15) developed catheter infections. One patient also developed bacteremia (patient no. 2) with *Klebsiella* spp. One patient (patient no. 6) developed typhlitis. Another patient (patient no. 10) developed oral mucositis. One patient (patient no. 17) became febrile (+39 C) with no source. Characteristic data of the conditioning regimen and ASCT course were shown in **Table 2**.

**Table 3** demonstrates the follow-up data on disease status after transplantation. Up to now, all patients are alive. At three months after transplantation, 13 patients had no residual disease (CR) in the following imaging evaluation which is mostly due to the conditioning regimen. Seven patients had residual disease even after the

conditioning regimen. Two patients (patient no. 4 and 15) had 3 cm and 1.9 cm lymphadenopathy, both in the right para-tracheal region. Patient number 5 BMT, Bone Marrow Transplantation had lymphadenopathy in the left supraclavicular region. Patients 8 and 11 had some lymphadenopathies with the largest diameter of 15 mm in the retroperitoneal region, plus mild splenomegaly (15.5 cm) and lymphadenopathies (17 mm and 18 mm) in the abdominal region, respectively. Patient number 13 had 1.5 cm lymphadenopathy in the para-aortic region. The patient number 14 had a 2.0 cm lymphadenopathy in the mediastinum. The median duration of follow-up for these patients was 25.9 months (9-51 months) after the transplantation. The median duration of treatment with Everolimus was 22.95 months (6-48 months). These patients were followed by clinical examination and laboratory data every three months and by imaging modalities (CT-Scan or PET-Scan) every three months for the first two years and then every six months thereafter. Only three patients (patient no 3, 14 and 16) relapsed 40, 36, 30 months after administration of everolimus respectively. All three of these patients received at least 2 years of everolimus maintenance therapy post transplantation. Two patients (no 8 and no 20) had positive PET Scans on follow up, but biopsies didn't show disease relapse. We administered Everolimus 10 mg once daily. In seven patients, there were some adverse effects that led to reducing the dose to 5

**Table 3. Characteristic data at follow-up**

Patient number	Post-transplant lymphoma status (before Everolimus administration)	Duration of therapy with everolimus in months up to the time of data extraction	Dose of Everolimus	Progression/Survival
1	CR	27	10 mg	None/Yes
2	CR	10	10 mg	None/Yes
3	CR	30	10 mg	Yes/Yes
4	PR	43	10 mg	None (stable disease)/Yes
5	PR	42	Started at 10 mg, then reduced to 5 mg	None (stable disease)/Yes
6	CR	13	Started at 10 mg, then reduced to 5 mg	None/Yes
7	CR	20	10 mg	None/Yes
8	PR	21	10 mg	None (stable disease)/Yes
9	CR	23	Started at 10 mg, then reduced to 5 mg	None/Yes
10	CR	13	10 mg	None/Yes
11	PR	16	10 mg	None (stable disease)/Yes
12	CR	8	10 mg	None/Yes
13	PR	22	Started at 10 mg, then reduced to 5 mg	None/Yes
14	PR	24	10 mg	Yes/Yes
15	PR	37	10 mg	None/Yes
16	CR	24	Started at 10 mg, then reduced to 5 mg	Yes/Yes
17	CR	41	Started at 10 mg, then reduced to 5 mg	None/Yes
18	CR	23	Started at 10 mg, then reduced to 5 mg	None/Yes
19	CR	19	Started at 10 mg, then reduced to 5 mg	None/Yes
20	CR	48	Started at 10 mg, then reduced to 5 mg	None/Yes

CR, Complete Response; PR, Partial Response

**Table 4. Hematologic and non-hematologic toxicity profile in patients receiving Everolimus**

Adverse effect	NCI Toxicity grade*	Number of cases
Non-Hematological		
Non-infectious Pneumonitis	Grade II	1
	Grade III	1
Stomatitis	Grade I	14
	Grade II	7
	Grade III	2
	Grade IV	1
Dyslipidemia	Grade I	3
Maculopapular rash	Grade I	6
	Grade II	2
Elevated ESR (up to 100 mm/h)	-	2
Elevated LDH (up to 1,000 IU/L)	-	8
Hematological		
Thrombocytopenia	Grade I	8
Neutropenia	Grade II	3
Anemia	Grade I	3

\*Grading was performed using common toxicity criteria version 1.0 (12)  
 NCI, National Cancer Institute; ESR, Erythrocyte sedimentation rate; LDH, Lactate dehydrogenase

mg daily.

The most notable adverse effects in these patients were as follows: Non-infectious pneumonitis (1 patient grade II and 1 patient grade III), stomatitis (2 patients grade III and 1 patient grade IV), neutropenia (3 pa-

tients with grade II). **Table 4**, demonstrates detected adverse effects related to everolimus during the course of this study.



## Discussion

### Suggestions for maintenance therapy in HL

In this study, we followed Everolimus efficacy and safety profile as an agent for post-ASCT maintenance therapy among 20 patients with high-risk Hodgkin lymphoma. To our knowledge this is one of the first phase II clinical studies to evaluate the efficacy and safety profile of Everolimus for HL patients in post-ASCT setting. In this study we recognized favorable outcomes. Only three patients out of the twenty high risk patients relapsed (15%), in other words, 85% did not show any disease progression. Relapse occurred after Everolimus discontinuation in all of these three patients. None of the patients who did not stop the drug, relapsed or progressed.

The AETHERA study was the first study that established a role for maintenance therapy for patients with primary refractory or relapsing Hodgkin lymphoma (HL) after autologous stem cell transplantation (ASCT)<sup>4</sup>. In the AETHERA study, Brentuximab Vedotin was administered within 30 to 45 days after ASCT in one arm and the results were compared to a control placebo arm with no maintenance therapy. The results were promising and PFS was improved to 42.9 months in the Brentuximab Vedotin arm in comparison with 24.1 months in the placebo arm<sup>4</sup>. A remaining question is whether if the patients who had received Brentuximab Vedotin as a salvage regimen besides chemotherapeutic agents would also benefit from this maintenance therapy, however, it may depend on how they responded to the initial treatment. In another study conducted by Jerjes Kort *et al.* 20 patients with relapsed or refractory Hodgkin lymphoma received Brentuximab Vedotin post-ASCT as a consolidation therapy every 3 weeks for 4 cycles<sup>13</sup>. After a median follow-up of 26.5 months, 3 patients progressed. The median time till relapse was 6 months among these 3 patients. The median PFS and OS at two years were 72% and 100% respectively with no significant toxicities. The PFS in this study was comparable to the AETHERA study in 2 years.

In addition to Brentuximab Vedotin, anti-PD-1 (programmed death 1) therapies had some effects on relapsing or refractory Hodgkin lymphoma. In a single-arm phase II study, patients received Pembrolizumab at the dose of 200 mg every 3 weeks for 8 cycles. Among 27 patients, 6 patients relapsed at a median of 8 months. The PFS and OS at the 18<sup>th</sup>- month evaluation was 78% and 100% respectively, with no mortality reported<sup>5</sup>. Another trial, NCT02362997, is now conducted for evaluating the efficacy of pembrolizumab as adjuvant treatment in these categories of patients.

### Mammalian Target of Rapamycin (mTOR) inhibitors as an alternative maintenance therapy

mTOR is a serine kinase and a key member of phosphatidylinositol 3-kinase (PI3K/AKT) signaling stream. It consists of two distinct subunits of mTOR complex 1 and 2 (mTORC1 and mTORC2). These subunits interact with molecular input signals that are induced by growth factors and nutritional supplies, and play a central role in cellular growth, proliferation and survival. Activated mTORC1 induces a downstream signaling that leads to phosphorylation of an inhibitory binding protein called 4E-BP1 (eukaryotic translation initiation factor 4E binding protein 1), and subsequently, to activation of two transcription promoting molecules, eIF4E (eukaryote initiation factor 4E) and S6K1 (ribosomal S6 protein kinase 1). These all lead to reinforced cellular protein synthesis. mTORC2 interacts with several kinases as well and is mostly involved in cytoskeletal structure. Numerous mechanisms can cause an unfavorable increase in PI3K/AKT/mTOR pathway activity and subsequently, cancer. In this regard, mTOR inhibition has been a strategic suggestion for cancer treatments. Sirolimus and Everolimus inhibit ribosomal protein S6 and also 4E-BP1 protein which leads to inhibition of mRNAs translation that leads to cell cycle arrest<sup>6, 14</sup>.

Furthermore, PI3K/Akt/mTOR pathway is an axis that is related closely to vascular endothelial growth factor (VEGF) and hypoxia-induced factor-1 $\alpha$  (HIF-1 $\alpha$ ). Activation of this pathway leads to an increment of HIF-1 $\alpha$  and also VEGF, which leads to angiogenesis especially via the substrate of mTOR. On the other hand, PI3K/Akt is a downstream pathway for VEGF and angiogenesis, proliferation and differentiation<sup>15</sup>. In Hodgkin lymphoma micro-vessel formation especially in early-stage disease<sup>16</sup>, occurs with this pathway and as shown by immunohistochemistry (IHC) staining, VEGF staining is increased in macrophages and other cells of the microenvironment of lymphomatous tissue<sup>17</sup>. The main stimulus for VEGF expression is hypoxia. Also, platelet-derived growth factor/Receptor (PDGF/PDGFR) axis plays a role in angiogenesis in lymphomatous tissues and its function correlates with mTOR<sup>18</sup>. Also, Fibroblast growth factor (FGF) may promote cell signaling, growth and angiogenesis that is expressed in Reed-Sternberg cells in Hodgkin lymphoma. FGF-2 induced lymph-angiogenesis through Akt/mTOR/P70-S6K1 pathway which can be blocked by mTOR inhibitors<sup>19</sup>.

Everolimus is a member of first-generation mTOR inhibitor with immunosuppressive and anti-proliferative activity. This drug increase G0 and G1 cells and decrease G2 and M phases in cell cycles<sup>20</sup>.

From a clinical point of view, Johnston *et al.* studied patients with relapsed Hodgkin lymphoma after ASCT or patients with relapsed disease who were ineligible

for ASCT. Of nineteen patients, the overall response rate (ORR) was 47%. Eight partial responses (PR), one complete response (CR) and eight stable diseases (SD) were observed<sup>11</sup>.

In another study that was conducted by Patrick B. Johnston *et al.*, they evaluated 57 patients from fourteen centers between 2009 and 2014. These patients were patients with Hodgkin lymphoma with progression after ASCT and or Gemcitabine, Vinblastine or Vinorelbine chemotherapy regimens. Everolimus was administered 10 mg in these patients. The ORR was 45.6% with five patients achieving CR and twenty-one patients achieving PR and twenty patients with stable disease<sup>21</sup>.

Nagler *et al.* randomized patients with post-ASCT Hodgkin lymphoma to receive Interleukin-2 (IL-2) and Interferon- $\alpha$  versus observation. There was no difference in OS and disease-free survival (DFS) between both arms<sup>22</sup>.

In this study, we evaluated patients with primary refractory or relapsing Hodgkin lymphoma who had undergone ASCT and received Everolimus thereafter as maintenance therapy. We have seen favorable results. Only 3 patients relapsed after a median of 22.95 months of follow-up.

This study was a single-arm study, hence, the efficacy of Everolimus should be evaluated in randomized control clinical trials with larger population studies. The important point is, that we had not any serious side effects of Everolimus. The mucocutaneous side effects were common; however, they were controlled easily.

In conclusion, we reported a case-series of patients with primary refractory or relapsing Hodgkin lymphoma who had undergone ASCT and had received Everolimus as maintenance therapy. The results in our study were promising, however, it needs studies with larger populations and different groups of maintenance therapy.

## Author Contributions

MM drafted original manuscript, and HAT, AH, HR and SZ reviewed it. SS helped to revise it, and all authors approved the final manuscript.

## Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

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