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Retrospective Study

# Outcome of Outpatient Autologous Hematopoietic Stem Cell Transplantation in Patients with Multiple Myeloma and Relapsed and Refractory Hodgkin Lymphoma. The Experience of King Fahad Specialist Hospital in Dammam, Saudi Arabia

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**Keywords:** Multiple myeloma; Hodgkin lymphoma; Autologous hematopoietic stem cell transplantation; Non-cryopreservation; Outpatient transplantation



## Abstract

**Background:** Autologous hematopoietic stem cell transplants (HSCT) is the standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (MM) and patients with relapsed and refractory Hodgkin lymphoma (R/R-HL) who achieve chemosensitivity after salvage therapy. Although autologous HSCT is routinely performed in an inpatient setting, the procedure can safely be performed in an outpatient setting.

**Methods and materials:** A retrospective study of patients with MM and R/R- HL who received outpatient autologous HSCT at King Fahad Specialist Hospital (KFSH) in Dammam, Saudi Arabia between the first of April 2017 and the 31st of January 2022 was performed.

**Results:** Over the study period of 4 years and 10 months, a total of 90 outpatient autologous HSCTs were performed for 79 patients (54 patients with MM; 4 of them received planned tandem autografts and 7 other myeloma patients received second autologous HSCTs for relapsed or progressive disease; and 25 patients with R/R-HL) at our institution. The median ages of patients with MM and those with R/R-HL at HSCT were 50.4 years and 27.8 years respectively.

At the presentation of their MM, the following high-risk (HR) features were encountered: stage II and III diseases according to the revised international scoring system (RISS) in 53.7%; adverse cytogenetics in 42.6% and extensive bone involvement in 53.7% of patients. In patients with HL at presentation, 48% of patients had stage IV disease according to Ann Arbor staging classification and 84% of patients had B symptoms.

Survival for 100 days post-HSCT for all patients with MM and HL who received outpatient autologous transplants was 100%. For patients with MM, the overall survival (OS) rates at 3 years and 4 years post-HSCT were 80% and 67%, while the progression-free survival (PFS) rates over 3 years and 4 years were 58% and 38% respectively. For patients with HL, the OS at 6 years post-HSCT was 95% while the PFS rates at 3 years and 6 years post-HSCT were 84% and 62% respectively.

**Conclusion:** Outpatient autologous HSCT for patients with MM and HL is safe, and feasible and can lead to short-term as well as long-term outcomes that are comparable to autologous transplantation performed in an inpatient setting. Additional benefits of outpatient autologous include saving beds and reducing hospital costs.

## Introduction

MM is characterized by the proliferation of monoclonal plasma cells in the bone marrow and the production of monoclonal proteins as well as the occurrence of secondary end-organ damage [1-7]. The recent utilization of various novel therapies such as proteasome inhibitors, immunomodulatory agents and monoclonal antibodies in the treatment of patients with newly diagnosed MM and relapsed disease has improved not only the depth and duration of disease response but also the OS [8,9]. In patients with newly diagnosed MM, VRd (bortezomib, lenalidomide and dexamethasone) regimen is recommended as the standard first-line treatment while in patients with HR-MM, the addition of daratumumab has been shown to improve the efficacy and prolong survival [4,7,10-13]. However, despite the use of several lines of novel therapies, MM has remained an incurable disease [14,15]. Hence, there is a need to: (1) develop novel targeting therapies with different mechanisms of action to achieve deep and durable responses in an attempt to cure MM; and (2) identify tumor intrinsic and extrinsic resistance mechanisms in order to direct the design of combinations of novel drugs that can prevent or overcome drug resistance to improve patient survival [14,15].

HL is an uncommon B-cell lymphoid malignancy that accounts for 10% - 15% of all lymphomas [16-18]. Although it mostly affects young individuals, HL has a second peak of incidence in patients > 60 years of age [18]. Approximately 80% of patients with HL can be cured with initial chemotherapy and radiotherapy. However, 10% -30% of patients relapse and 5% - 10% of patients develop refractory disease [16,19-22]. Initial treatment of HL is based on: the histology of the disease, anatomical stage, and presence or absence of poor prognostic features [17]. The incorporation of functional imaging in the management of HL allows adjustment or modification of treatment and identifies patients who may benefit from additional therapeutic interventions such as radiotherapy [23]. Currently, positron emission tomography (PET)-adapted chemotherapy and radiotherapy approaches are utilized in the initial treatment of early-stage HL and have resulted in OS and PFS of 95% and 85% respectively [24,25]. Novel agents including the antibody-drug conjugate brentuximab vedotin (BV) and the checkpoint inhibitors such as nivolumab and pembrolizumab can improve the effectiveness of HL treatment and have been shown to extend OS in patients with R/R-HL [16,22,23,26,27]. However, in patients with advanced disease, early incorporation of novel therapies even in the frontline regimens may improve the outcome of these patients who carry poor prognoses [24,28,29].

In patients with R/R-HL, several regimens of chemotherapy and novel agents have been employed as salvage therapy including (1) dexamethasone + BEAM (BCNU, etoposide, cytarabine, melphalan) or mini-MEAM that includes all the chemotherapeutic agents included in BEAM regimen but with dose reductions; (2) ICE (ifosfamide, carboplatin, etoposide); (3) DHAP (dexamethasone, cytarabine, cisplatin); (4) ESHAP (methylprednisolone, cisplatin, etoposide, cytarabine); (5) MINE (mitoguazone, ifosfamide, vinorelbine, etoposide); (6) GDP (gemcitabine, dexamethasone, cisplatin) or GVD (gemcitabine, dexamethasone, liposomal doxorubicine); (7) IV (ifosfamide, vinorelbine) or IEV (ifosfamide, etoposide, vinorelbine); and (8) BV-based therapies such as BV + checkpoint inhibitors; BV + bendamustine (BVB); BV + ICE; and BV + dexamethasone + HD cytarabine + cisplatin [30-41]. However, there is no obvious superior salvage regimen although maintaining dose intensity is important for optimal responses [42]. Nevertheless, the use of a DICEP regimen (dose-intensive cyclophosphamide + etoposide + cisplatin) has been shown to be feasible, well tolerated, and effective with favorable long-term outcomes when used as salvage as well as stem cell mobilization regimen prior to high-dose (HD) chemotherapy and autologous HSCT in patients with lymphoma [43-45]. In patients with R/R HL, a DICEP regimen of chemotherapy can lead to excellent long-term outcomes that may be superior to the less intensive salvage regimens [43-45]. GDP regimen which is used as salvage therapy in patients with R/R HL has a high response rate, favorable toxicity profile, and excellent mobilization potential. Additionally, it can safely be administered in an outpatient setting [46].

## Methods and materials

A retrospective study was conducted between the 1st of April 2017 and the 31st of January 2022. The medical records, the clinical data as well as the laboratory data of all patients with MM and HL who received autologous HSCT at KFSH in Dammam, Saudi Arabia during the time specified above were retrieved for analysis. For our cryopreserved autologous HSCTs, after controlling the primary disease using certain induction therapeutic regimens, mobilization of stem cells was performed using cyclophosphamide, ESHAP, DHAP, DICEP, or filgrastim alone, then the collection of mobilized stem cells by apheresis was done followed by cryopreservation of the apheresis product. After the administration of HD melphalan or other conditioning therapies, the cryopreserved stem cells were infused after thawing. However, for non-cryopreserved autologous grafts, the same process was followed with the exception of keeping the collected stem cells at 4 ºC for 24 to 72 hours instead of cryopreserving them. Then the fresh stem cells were infused within 24 hours after administration of HD melphalan or other conditioning regimens.

During stem cell mobilization, once the CD34+ cell count in peripheral blood exceeded 10.0 to 20.0 × $10^6$/kg body weight, stem cell collection by leukapheresis was usually commenced. We aimed to obtain a target of 3.0 to 4.0 × $10^6$ CD34+ cells/kg in case a single auto-HSCT was desired and a target of 6.0 to 8.0 × $10^6$ CD34+ cells/kg in case a tandem transplant for MM was planned. After day 0 of autologous HSCT, prophylactic antimicrobials were administered, and starting from day 5 post-HSCT till the day of neutrophil engraftment daily doses of filgrastim were administered.

### Statistical analysis

The SSPS version 22 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Kaplan-Meier method with a log-rank test was used to estimate the survival rates and to identify risk factors that influenced the treatment outcome. OS was defined as the duration from the day of graft infusion until death or the date of the last follow-up for live patients. PFS was defined as the period from graft infusion till the documentation of disease relapse/progression or last follow-up for the non-relapsed/progressed patients.

## Results

During the study period, 4 years and 10 months, a total of 90 outpatient autologous HSCTs were performed for 79 patients (54 with MM and 25 patients with HL) at KFSH in Dammam, Saudi Arabia. Single autologous grafts were offered to all 25 patients with HL and 54 patients with MM. Four MM patients received planned tandem autologous HSCTs while 7 other myeloma patients received second autologous grafts due to relapse or progression of their MM after receiving appropriate salvage therapies. Out of the 79 recipients of outpatient autologous HSCT, there were 41 males and 38 females and the median age of patients at HSCT was 50.4 years for MM patients and 27.8 years for patients with HL.

In patients with MM at the presentation of their disease, the following HR features were encountered: stage II and III diseases according to the RISS in 53.7% of patients, adverse cytogenetics in 42.6% and extensive bone involvement in 53.7% of patients, while 11.20% of patients had either renal dysfunction or end-stage renal disease (ESRD) (Tables 1-4). Out of the 65 outpatient autologous HSCTs, 39 autologous HSCTs (60.0%) were performed using non-cryopreserved stem cells while 26 autologous grafts (40.0%) used cryopreserved stem cells. Regarding the initial therapy administered to MM patients, 46 patients (85.2%) of our patients received bortezomib-based therapy either the doublet regimen bortezomib and dexamethasone (VD) or one of the triplet regimens [VRd; bortezomib, cyclophosphamide, dexamethasone (VCD); or bortezomib, thalidomide, dexamethasone (VTD)] and only 6 patients (11.1%) received more intensive regimens containing PACE chemotherapy (cisplatin, doxorubicin, cyclophosphamide, and etoposide) including VTD-PACE, VRd-PACE and carfilzomib, lenalidomide, dexamethasone (KRd)-PACE (Table 5). The number of lines of chemotherapy administered prior to autologous HSCT was as follows: 40 patients (74.1%) received 1 line of therapy, 8 patients (14.8%) received 2 lines of therapy, while 6 patients (11.1%) received ≥ 3 lines of chemotherapy. Treatment responses in MM patients before outpatient autologous HSCT were as follows: 4 patients (7.4%) achieved partial response (PR), 33 patients (61.1%) achieved very good PR (VGPR) and 16 patients (29.6%) achieved complete response (CR) while only 1 patient (1.9%) achieved stringent CR. Regarding the maintenance therapy administered to patients with MM after outpatient autologous HSCT, 6 patients (11.1%) received maintenance therapy for 1 to 2 years and 44 patients (81.5%) received maintenance treatment till disease progression, while 4 patients (7.4%) did not receive maintenance therapy.

**Table 1:** Stage of disease in patients with MM subjected to outpatient auto-HSCT.

| Stage | Number | Percentage |
|---|---|---|
| I | 23 | 42.6 |
| II | 19 | 35.2 |
| III | 10 | 18.5 |
| Unknown | 2 | 3.7 |

•MM: Multiple Myeloma; •auto-HSCT: autologous Hematopoietic Stem Cell Transplantation

**Table 2:** Cytogenetic abnormalities in patients with MM subjected to outpatient auto-HSCT.

| Cytogenetic abnormality | Number | Percentage |
|---|---|---|
| Normal | 18 | 33.3 |
| Chromosome 3 abnormalities including deletion of chromosome 3 | 5 | 9.25 |
| 17 p Deletion | 5 | 9.25 |
| Translocation of chromosome 14 including: t 4,14; t 6,14; t 14,16; t 14,20 | 9 | 16.7 |
| Trisomies of chromosomes: 3,7,9,15,17 | 7 | 13.0 |
| Monosomies of chromosomes: 13; 16 | 4 | 7.4 |
| Not available; Unknown | 6 | 11.1 |

•MM: Multiple Myeloma; •auto-HSCT: autologous Hematopoietic Stem Cell Transplantation

**Table 3:** Bone lesions in patients with MM subjected to outpatient auto-HSCT.

| Type of Bone Involvement | Number | Percentage |
|---|---|---|
| Localized or single lytic lesion (s) | 8 | 14.8 |
| Multiple lytic lesions | 24 | 44.4 |
| Pathological fractures requiring surgery | 5 | 9.3 |
| Osteopenia | 17 | 31.5 |

•MM: Multiple Myeloma; •auto-HSCT: autologous Hematopoietic Stem Cell Transplantation

**Table 4:** Renal dysfunction in patients with MM subjected to outpatient auto-HSCT.

| Type of renal dysfunction | Number | Percentage |
|---|---|---|
| End stage renal disease (ESRD) on hemodialysis [serum creatinine: 629 -1328 µmol/L] Creatinine clearance < 10 mL/minute | 2 | 3.7 |
| ESRD not yet on hemodialysis [serum creatinine: 381- 477 µmol/L] Creatinine clearance: 10-20 mL/minute | 1 | 1.9 |
| Significant renal dysfunction [serum creatinine: 185 - 204 µmol/L] Creatinine clearance: 20-30 mL/minute | 3 | 5.6 |

• MM: Multiple Myeloma; • auto-HSCT: autologous Hematopoietic Stem Cell Transplantation

**Table 5:** Initial therapy given to patients with MM subjected to outpatient auto-HSCT.

| Regimen/Protocol | Number of patients | Percentage |
|---|---|---|
| Bortezomib + Dexamethasone [VD] | 10 | 18.5 |
| Bortezomib triplet protocols VTD/VCD/VRd | 36 | 66.7 |
| Lenalidomide + dexamethasone [RD] | 2 | 3.7 |
| More intensive regimens VTD-PACE / VRd-PACE / KRd-PACE | 6 | 11.1 |

MM: Multiple Myeloma; Auto-HSCT: autologous Hematopoietic Stem Cell Transplantation; VCd: bortezomib, cyclophosphamide, dexamethasone; VTd: bortezomib, thalidomide, dexamethasone; VRd: bortezomib, lenalidomide, dexamethasone; VTD-PACE: bortezomib, thalidomide, dexamethasone, cisplatin, adriamycin, cyclophosphamide, etoposide; KRd: carfilzomib, lenalidomide, dexamethasone.

Out of the 25 patients with HL subjected to outpatient autologous HSCT, there were 14 males and 11 females and their ages ranged between 16 and 52 years with a median age of 27.8 years at the time of HSCT (Table 6). Regarding the histological subtypes: 12 patients (48%) had nodular sclerosis classical HL, while 6 patients (24%) had mixed cellularity subtypes. Additionally, 12 patients (48%) had stage IV disease at presentation, 21 patients (84%) had B symptoms, and 4 patients (16%) had the bulky disease and another 4 patients (16%) had the disease at extranodal sites (Table 6). Several salvage regimens of chemotherapy were given to HL patients at the relapse or progression of their disease. Seventeen patients (68%) required a single line of salvage therapy while 8 patients (32%) had 2-5 lines of salvage treatment. Two to four cycles of BVB were given to 10 patients (40%), while 1 cycle of ESHAP chemotherapy was given to 2 patients (8%) and 1 cycle of DICEP was given to 5 patients (20%) (Table 7). Five different stem cell mobilization regimens were used in patients with HL subjected to outpatient autologous HSCT and these included: cyclophosphamide in 9 patients (36%), DICEP in 8 patients (32%), ESHAP in 4 patients (16%), DHAP in 2 patients (8%) and granulocyte-colony stimulating factor (G-CSF) alone in 2 patients (8%) (Table 8). The following early post-HSCT complications were encountered in HL patients: febrile neutropenia (FN) in 8 patients (32%), infectious complications in 4 patients (16%) and mucositis in 2 patients (8%) (Table 9). The median days of engraftment for neutrophils and platelets for patients with R/R-HL were 12 days and 13 days post-HSCT respectively (Figure 1).

Survival at day 100 post-HSCT for all patients with MM and HL who received their outpatient autologous HSCTs was 100%. Also, the long-term outcomes of our patients were excellent. For patients with MM subjected to outpatient autologous HSCT, the OS rates at 3 years and 4 years post-HSCT were 80% and 67%, while PFS rates over 3 years and 4 years were 58% and 38% respectively (Figure 2). For patients with HL subjected to outpatient autologous HSCT, the OS at 6 years post-HSCT was 95% while PFS rates at 3 years and 6 years post-HSCT were 84% and 62% respectively (Figure 3).

**Table 6:** Pre-treatment characteristics of patients with HL subjected to outpatient autologous HSCT.

| Characteristic | Details |
|---|---|
| Age | Range: 16-52 |
| Gender | Males: 14; Females: 11 |
| Classical HL subtype | Nodular sclerosis: 12 (48%)<br>Mixed cellularity: 6 (24%)<br>Unclassified: 7 (28%) |
| Disease stage at diagnosis | II: 7 (28%); III: 6 (24%); IV: 12 (48%) |
| B symptoms | 21 (84%) |
| Bulky disease | 4 (16%) |
| Extranodal sites | 4 (16%) |

•HL: Hodgkin Lymphoma; •HSCT: Hematopoietic Stem Cell Transplantation

**Table 7:** Salvage therapy given for disease progression or relapse in patients with HL subjected to outpatient auto-HSCT.

| Complication | Specific regimens | Number | Percentage |
|---|---|---|---|
| Single line of salvage therapy | ESHAP (1 cycle) | 2 | 8 |
| | DICEP (1 cycle) | 5 | 20 |
| | BVB (2-4 cycles) | 10 | 40 |
| Combined therapy [2-5 lines of various combinations of the following regimens: ESHAP; DHAP; DICEP; BVB; NIVO; IGEV] | 2 lines | 6 | 24 |
| | 3 lines | 1 | 4 |
| | 4 lines | 1 | 4 |

•HL: Hodgkin Lymphoma; •auto-HSCT: autologous Hematopoietic Stem Cell Transplantation; •ESHAP: Methylprednisolone, Cisplatin, Etoposide, Cytarabine; •DHAP: Dexamethasone, Cytarabine, Cisplatin; •DICEP: Dose-IntensiveCyclophosphamide, Etoposide, Cisplatin; •BVB: Brentuximab Vedotin; •IGEV: Ifosfamide, Gemcitabine and Vinorelbine; • NIVO: Nivolumab

**Table 8:** Stem cell mobilization regimens used in patients with HL subjected to outpatient auto-HSCT.

| Regimen | Number | Percentage |
|---|---|---|
| DICEP | 8 | 32 |
| Cyclophosphamide | 9 | 36 |
| ESHAP | 4 | 16 |
| DHAP | 2 | 8 |
| G-CSF alone | 2 | 8 |

•HL: Hodgkin Lymphoma; •auto-HSCT: autologous Hematopoietic Stem Cell Transplantation; •DICEP: Dose-Intensive Cyclophosphamide, Etoposide, Cisplatin; •ESHAP: Methylprednisolone, Cisplatin, Etoposide, Cytarabine; •DHAP: Dexamethasone, Cytarabine, Cisplatin; •G-CSF: Granulocyte Colony Stimulating Factor

**Table 9:** Post-transplant complications encountered in patients with HL subjected to outpatient auto-HSCT.

| Complication | Number | Percentage |
|---|---|---|
| Febrile neutropenia | 8 | 32 |
| Mucositis | 2 | 8 |
| Infectious complications | 4 | 16 |
| No complications | 2 | 48 |

•HL: Hodgkin Lymphoma; •auto-HSCT: autologous Hematopoietic Stem Cell Transplantation

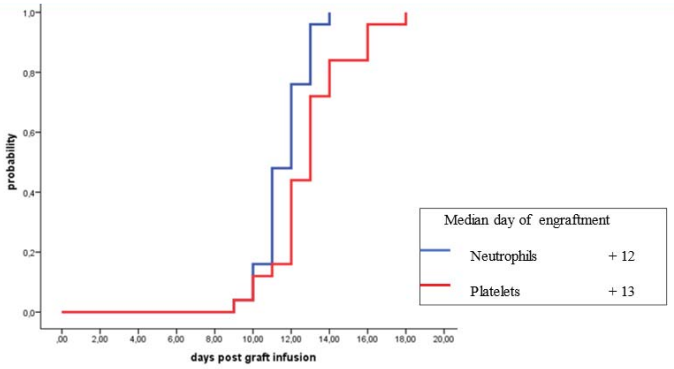


**Figure 1:** Engraftment of neutrophils and platelets in patients with relapsed/refractory Hodgkin lymphoma autografted with single agent high dose melphalan

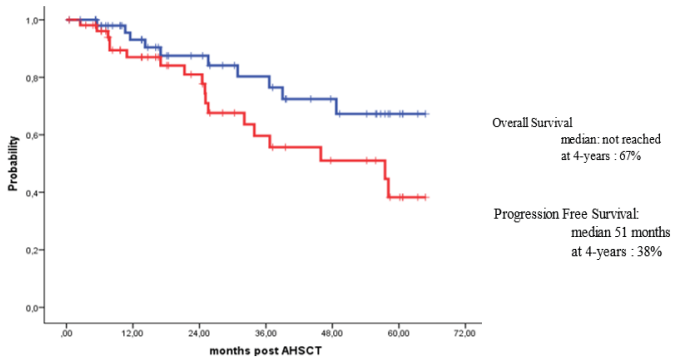


**Figure 2:** Overall and survival free survival for patient with Multiple myeloma autografted in outpatient basis.

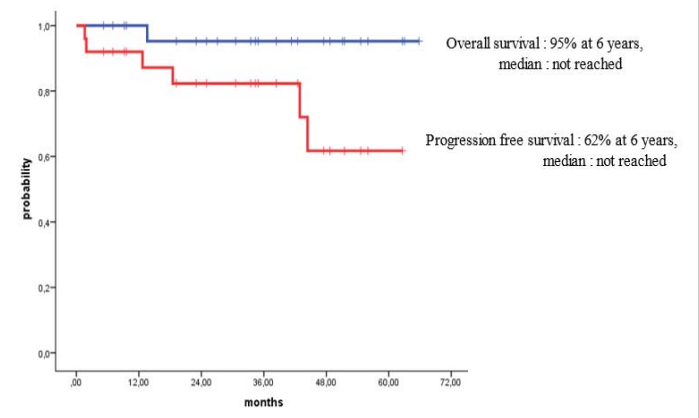


**Figure 3:** Overall and Progression free survival for patients with relapsed/refractory Hodgkin lymphoma autografted with single agent high dose melphalan.

## Discussion

Autologous HSCT is a widely accepted therapeutic strategy for the treatment of certain hematologic malignancies (HMs) and it is most frequently indicated for patients with MM and lymphoma [9,47]. However, eligibility for autologous HSCT is determined by several factors including age, performance status, presence and severity of comorbid medical conditions, and frailty score as frailty has been shown to be a predictor of short survival and is considered an exclusion criterion for autologous HSCT [7,8,48,49]. Cryopreservation using the cryopreservative dimethyl sulfoxide is routinely employed after stem cell collection prior to autologous HSCT [3,7,50]. However, several old and recent studies in addition to one systematic review have shown that autologous HSCT using non-cryopreserved stem cells is safe, cost-effective and leads to short-term as well as long-term results that are at least equivalent to autologous HSCT using cryopreserved stem cells [7,47,50-55]. One of the advantages of autologous HSCT without cryopreservation is the simplicity of its implementation which allows the performance of autologous HSCT as an outpatient [3,7,56]. In our 65 outpatient autologous HSCTs performed for patients with MM, non-cryopreserved stem cells were used in 39 autografts (60.0%), while cryopreserved stem cells were given to the other 40% of HSCTs, particularly in the tandem or second autologous grafts.

Despite the availability of several lines of novel agents, autologous HSCT is still considered the standard of care in the treatment of patients with MM who are eligible for transplantation [2,7,8,13,57]. The standard conditioning regimen for patients with MM undergoing autologous HSCT is HD melphalan (200 mg/m$^2$) given intravenously (IV) [5,7,8,13,58]. However, in patients with renal dysfunction or failure, dose reductions to 100 mg/m$^2$ - 140 mg/m$^2$ are needed according to creatinine clearance [5,7]. In our study, HD melphalan was the conditioning therapy given to our MM patients. However, melphalan dose adjustments were offered to patients having creatinine clearance < 20 mL/minute at the time of autologous HSCT. After stem cell mobilization with cyclophosphamide, G-CSF and plerixafor which is used in case of poor mobilization, peripheral blood stem cells are collected using an apheresis machine aiming to collect at least 2.5 x 10$^6$/kilogram body weight to guarantee successful autologous graft [3,13,47].

HD chemotherapy and autologous HSCT can salvage 40% - 70% of patients with R/R HL [59]. Hence, salvage therapy followed by HD chemotherapy and autologous HSCT has become the standard of care for most patients with primary refractory disease or those who relapse after initial therapy [16,17,19-21,60]. In patients with R/R HL, studies have shown that HD chemotherapy followed by autologous HSCT can lead to 5 years of OS of 55% to 63% and 5 years of PFS and event-free survival (EFS) of 44% and 51.3% respectively [61,62]. However, the use of BV and checkpoint inhibitors after autologous HSCT in patients with R/R HL has further improved the long-term outcomes with 5 years of PFS ranging between 59% and 73.4% and 5 years OS reaching 92% [25,63,64].

In patients with lymphoma, BEAM conditioning therapy has traditionally been administered over 6 days as an inpatient [60,65]. Studies have shown that the BEAM regimen can safely be administered in an outpatient setting in order to: reduce costs and length of hospitalization, decrease risks of severe toxicities and infectious complications, and improve patient satisfaction and quality of life [60,65]. In patients with HL, several other chemotherapeutic regimens have been employed in the conditioning therapy prior to autologous HSCT as alternatives to BEAM chemotherapy and these include: (1) a mini-BEAM regimen, (2) the addition of rituximab or anti-CD 25 radioimmunotherapy to BEAM regimen, (3) modification of BEAM regimen such as the use of TEAM regimen (thiotepa, etoposide, cytarabine, melphalan) and (4) replacing BEAM chemotherapy by other regimens such as BEC (BCNU, etoposide, cyclophosphamide); etoposide and melphalan; mitoxantrone and melphalan; as well as busulfan, cyclophosphamide, and etoposide [66-77]. Studies have shown that the use of HD melphalan alone given as conditioning therapy prior to autologous HSCT in patients with advanced or R/R HL has the following advantages: (1) being adequate and cost-effective with outcomes that are comparable to multiagent chemotherapeutic regimens such as BEAM, (2) less exposure to other toxic chemotherapies, and (3) allowing autologous HSCT to be performed in an outpatient setting [78-81]. In our patients with R/R-HL, HD melphalan proved to be an adequate conditioning therapy and it allowed outpatient autologous HSCT to be performed.

In patients with R/R HL, particularly those who relapse after autologous HSCT but have a chemo-sensitive disease, allogeneic HSCT may be the only potentially curative modality of treatment that can offer long-term survival [21,82]. HD BEAM administered as an inpatient for 6 consecutive days has traditionally been used as conditioning therapy given

prior to autologous HSCT in patients with lymphoma [60,65]. However, outpatient administration of the BEAM regimen has been shown to be safe and can offer several advantages including reductions in the length of hospitalization and costs [60].

While historically, due to logistic issues and concerns regarding toxicities and infections, most of the autologous HSCTs were performed in an inpatient setting, the swift recovery after peripheral autologous HSCT and improvements in supportive care have enabled patients to receive autologous HSCT at outpatient [83,84]. It has been reported that outpatient autologous HSCT is safe and feasible in patients with lymphoma, central nervous system tumors, and breast cancer [83,85-87]. Allogeneic HSCT with reduced intensity conditioning therapy as well as haploidentical allogeneic HSCT have been performed in an outpatient setting in the following diseases: MM; R/R lymphoma; Sezary syndrome; and other R/R HMs [88-94]. Even total body irradiation has been given successfully in an outpatient setting [94].

Due to the ease of administration of HD melphalan, the relatively low extra-hematological toxicity, and the short period of neutropenia, patients with MM are ideal candidates for outpatient autologous HSCT [95-97]. Additionally, several studies have shown that autologous HSCT can safely be performed in an outpatient setting in patients with HL and non-Hodgkin lymphoma in order to save healthcare resources without compromising patient outcomes [65,85,98-100]. With daily outpatient clinical evaluation and intensive supportive care; outpatient autologous HSCT is safe, feasible, and cost-effective. Also, it can lead to excellent short-term and long-term outcomes in carefully selected patients with MM and lymphoma [83,97,101-114]. However, it is essential to have HSCT- specific supportive interventions that address the multidisciplinary and complex requirements of both patients and their caregivers by optimising the involvement of the key stakeholders throughout the entire process from stem cell mobilization to passing the first 100 days post-HSCT [115]. Therefore, a multidisciplinary approach with close follow-up is required to guarantee a successful outcome of the autologous outpatient HSCT program [105,106,113,116].

Several studies have clearly indicated that outpatient HSCT has certain inclusion criteria that include: (1) availability of full-time caregiver; (2) good performance status; (3) favorable comorbidity profile; (4) residence within 20 to 30 minutes drive from the hospital; (5) stable psychological status; (6) patient preference; (7) expected compliance; and (8) signed written consent [83,97,101,102,107,114]. On the other hand, the exclusion criteria of outpatient HSCT include: (1) age more than 65 years; (2) performance status > 1; (3) lack of caregiver; (4) > 1-hour drive distance between home and hospital; (5) advanced disease such as MM or lymphoma (6) advanced comorbid medical conditions; (7) severe impairment of organ functions; (8) serious infection either encountered recently or not completely eradicated; (9) colonization with multidrug-resistant bacteria or fungus; and (10) no guaranteed availability of quick readmission to the hospital once hospitalization is needed [84,96,109,117]. In our study, we followed the inclusion and exclusion criteria outlined above for selecting patients to be candidates for outpatient autologous HSCT for patients with MM and R/R- HL.

The risk factors that can predict admission in recipients of outpatient autologous HSCT include (1) advanced disease, (2) female gender, (3) poor performance status, (4) low serum albumin level, and (5) more intensive conditioning regimens such as BEAM chemotherapy [84]. Indications for admission in recipients of outpatient HSCT include (1) severe mucositis requiring narcotic analgesia or total parenteral nutrition (TPN); (2) FN; (3) poor oral intake or uncontrolled nausea, vomiting, or diarrhea requiring TPN or aggressive hydration; (4) inability of family or caregiver to cope; (5) declining performance status of the patient; and (6) presence of other serious complications such as pneumonia, sepsis or arrhythmia [84,106,109-112,118]. Between 8% and 84% of recipients of outpatient autologous HSCT require hospitalization in the first 100 days post-HSCT ranges [84,103,106,109-113,119]. Duration of hospitalization ranges between 4 and 9 days and the most frequent day of unexpected hospitalization is day 7 post-autologous HSCT [103,105,106,110,112]. In our patients, readmission rates after HSCT were higher for patients with R/R-HL than patients with MM. In both groups of patients, mucositis, FN and infectious complications were the main reasons for readmissions. Additionally, vacant hospital beds were made available to guarantee the safety of patients transplanted in an outpatient setting.

The reported median time to engraftment in patients with MM receiving autologous HSCT at outpatient is 9-14 days for neutrophils and 12-19 days for platelets [106,108-112]. In our patients with MM, the median time for neutrophil engraftment with G-CSF given from the 5th-day post-HSCT onwards was 11 days while the median time for platelet engraftment post autologous HSCT was 17 days. However, in patients with R/R-HL, the median days of engraftment for neutrophils with G-CSF were given from day 5 post-HSCT onwards and platelets were 12 days and 13 days post-HSCT respectively (Figure 1). The reported transplant-related mortality (TRM) in recipients of autologous transplantation performed in an outpatient is 0.0% - 1.1% [96,101,103,106,111-114,116]. In our study, TRM at day 100 post-HSCT was 0.0% for patients with MM and patients with R/R-HL.

Outpatient autologous HSCT has several advantages that include: (1) significant reduction in costs; (2) alleviation of constraints of chronic bed shortage; (3) significantly lower overall resource utilization; (4) patient convenience and high patient satisfaction; (5) lower rate of infectious complications; and (6) lower rates of morbidity as well as TRM [96,102,105, 109,113,116,120,121]. Reductions in treatment costs, saving

hospital beds, and convenience as well as the satisfaction of patients were the main advantages of our outpatient autologous HSCT program.

In patients with MM, maintenance therapy after autologous HSCT has been shown to deepen and prolong responses and increase OS and PFS [122]. Lenalidomide maintenance given after autologous HSCT till disease progression had become the standard of care in patients with newly diagnosed MM as it has been shown to prolong PFS and EFS [123-126]. Bortezomib maintenance therapy after autologous HSCT in MM patients has been shown to be safe, well tolerated, and efficacious particularly in patients with: HR cytogenetics including deletion 17p, renal insufficiency, inability to tolerate lenalidomide, and those with a previous history of another cancer [127-129]. Compared to the traditional fixed-duration approaches, the evolving paradigm of continuous therapy and maintenance treatment offers prolonged disease control and improved outcomes in patients with MM. Currently, continuous therapy till disease progression represents the standard approach for patients with MM both at diagnosis and at relapse [130]. In our patients with MM, maintenance therapy with variable duration was given to 47 patients (87.04%).

The AETHERA trial (phase III randomized, placebo-controlled trial that included 325 patients with HL and was performed at 78 sites in USA and Europe between April 6, 2010 and September 21, 2012) showed that early consolidation with BV after autologous HSCT significantly improved PFS in patients at risk of relapse or progression following HSCT [131]. Subsequently, 2 other clinical trials performed in patients with HR or R/R HL showed that BV maintenance therapy following autologous HSCT improved the 2-year PFS between 67.75% and 75% [132,133]. Hence, it is recommended to intervene early by administering BV or other novel agents in patients with HL who are at risk of relapse or progression following autologous HSCT in order to improve their outcome [134-136]. In our patients with R/R-HL, maintenance therapy with a BV regimen was given to 5 patients (20%) while post-HSCT radiotherapy was offered to 7 patients (28%).

## Conclusion

Our patients developed MM and HL at a much younger age than in western countries. Significant proportions of our patients presented with HR features such as advanced disease stage. Outpatient autologous HSCT has specific inclusion and exclusion criteria and requires daily clinical evaluation, and intensive supportive care including correction of electrolytic disturbances, and administration of needed blood products and antimicrobials.

Autologous HSCT performed in an outpatient setting is safe, and feasible and leads not only to excellent short-term results but also to long-term outcomes that are at least comparable to the standard inpatient autologous transplantation. Conditioning therapy with HD melphalan and the use of non-cryopreserved autologous stem cells allowed us to perform autologous transplantation in outpatient settings. Advantages of performing outpatient autologous HSCT include saving beds, reducing hospital costs, and lowering the rates of infections and TRM.

### Authors' contributions

All authors participated in the management of the patients included in the study. Also, all authors read and approved the final form of the manuscript.

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