Retrospective Study

The outcome of autologous hematopoietic stem cell transplantation in patients with multiple myeloma. The experience of King Fahad Specialist Hospital in Dammam, Saudi Arabia

Khalid Ahmed Al-Anazi1*, Mutahar E1, Abduljalil O1, Kanfer S1, Kaloyannidis P1, Estanislas A1, Apostolidis I1, Almokhtar N1, Darweesh M1, Abdulbaqi M1, Alenazi W1, Alshammasi Z1, Alshaibani Z1, Kawarie M1, Raslan H2, Albahrani A3, Alsaber A2, AlMulhem N3, Dridi W4, Ayyad A1, Abu Rahma F1, Lardizabal J1, Salam A3, Haque K3, Alenazi W1, and Alhashmi H1

1Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, PO Box: 15215, Dammam 31444, Saudi Arabia
2Hematopathology and Flowcytometry, Department of Pathology and Central Laboratory, King Fahad Specialist Hospital, P.O. Box: 15215, Dammam 31444, Saudi Arabia
3Apheresis and Blood Bank, Department of Pathology and Central Laboratory, King Fahad Specialist Hospital, P.O. Box: 15215, Dammam 31444, Saudi Arabia
4Cytogenetics, Department of Pathology and Central Laboratory, King Fahad Specialist Hospital, P.O. Box: 15215, Dammam 31444, Saudi Arabia

Abstract

Background: Autologous hematopoietic stem cell transplants (HSCT) is the standard of care for newly diagnosed patients with multiple myeloma (MM) who are eligible for autologous transplantation. Although cryopreservation is routinely employed, autologous HSCT can be performed using non-cryopreserved stem cells.

Methods and materials: A retrospective study of patients with MM who received autologous HSCT between the 10th of October 2010 and the 31st of January 2022 at King Fahad Specialist Hospital (KFSH) in Dammam, Saudi Arabia was performed.

Results: Over 11 years and 113 days, a total of 135 autologous HSCTs were performed for 119 patients with MM at our institution. Single autologous HSCTs were performed for 119 patients, while 16 of these patients received either planned tandem autologous transplants or second autografts due to either progression or relapse of their myeloma. The median age of patients with MM at autologous HSCT was 51.5 years. At presentation of their MM, the following high-risk (HR) features were encountered: stage III disease according to the revised international scoring system (RISS) in 12.3%; adverse cytogenetics in 31.93% of patients; advanced bone disease in 60.50%; and renal dysfunction or failure in 11.76% of patients.

A total of 104 autologous HSCTs (77.04%) were performed without cryopreservation while 31 autografts (22.96%) were performed using cryopreserved apheresis stem cell products. Additionally, 54 autologous HSCTs (40.00%) were performed in an inpatient setting. Survival for 100 days post-HSCT for all patients with MM who received autologous transplants including those done at outpatient was 100%. The 4 years overall survival (OS) and progression-free survival (PFS) for patients with MM who received non-cryopreserved or fresh autologous HSCTs were 82% and 68% respectively.

Conclusion: Autologous HSCT without cryopreservation is safe, and feasible and can lead to short-term as well as long-term outcomes that are comparable to autologous transplantation with cryopreservation. Non-cryopreserved autologous grafts allow the performance of autologous transplants in an outpatient setting to save beds and reduce costs.
**Introduction**

MM, the second commonest hematologic malignancy, is characterized by the proliferation of monoclonal plasma cells in the bone marrow, production of monoclonal proteins, and occurrence of secondary end-organ damage [1-7]. MM is a disease of old age with the median age at diagnosis ranging between 65 and 74 years in the United States of America (USA) and Europe [2,3,8,9]. The global 5 years survival has more than doubled over the past 2 decades due to the availability of various lines of the novel therapeutic agents and HSCT, the recent advancements in diagnostic techniques, and the general improvement in health care [9-11]. The definition of HR-MM implies the presence of any of the following: stage III disease according to the RISS including high serum levels of β-microglobulin and lactate dehydrogenase as well as HR cytogenetics such as del(17p), t(4;14), t(14;16) and chromosome 1 abnormalities; plasma cell leukemia; extramedullary disease; and renal failure [5-9]. In patients with MM who are eligible for autologous HSCT, 3-4 cycles of induction therapy that consists of either bortezomib, lenalidomide, dexamethasone (VRd) or bortezomib, cyclophosphamide, dexamethasone (VCD), or bortezomib, thalidomide, dexamethasone (VTD) are usually given followed by single autologous HSCT [5,8,9]. However, in patients with HR disease it is recommended to give induction therapy with either daratumumab, bortezomib, lenalidomide, dexamethasone (Dara-VRd) or carfilzomib, lenalidomide, dexamethasone (KRd) as alternatives to VRd followed by single or tandem autologous HSCT [5,8].

In autologous HSCT, cryopreservation of hematopoietic stem cells is routinely employed. The standard and the most commonly used cryopreservative is dimethyl sulfoxide (DMSO) which prevents freezing damage to living cells [3,7]. DMSO is generally safe and nontoxic but its use is associated with significant side effects that include nausea, vomiting, abdominal cramps, hemolysis, as well as systemic adverse reactions. After cryopreservation and thawing of stem cells, 20% - 30% of the collected stem cells become nonviable due to early irreversible apoptosis [3].

A large number of studies from various parts of the world and one meta-analysis have shown that non-cryopreserved autologous HSCT for MM is not only simple, safe, and cost-effective but also can give results that are at least equivalent to autologous HSCT with cryopreservation [3,7]. This retrospective study was carried out to explore the short-term as well as the long-term outcomes of patients with MM subjected to autologous HSCT, particularly those receiving non-cryopreserved autologous grafts.

**Methods and materials**

A retrospective study was conducted between the the 10th of October 2010 and the 31st of January 2022. The medical records, clinical data as well as laboratory data of all patients with MM who received autologous HSCT at KFSH in Dammam, Saudi Arabia during the time period 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 and filgrastim, then collection of mobilized stem cells by apheresis was done followed by cryopreservation of the apheresis product. After administration of high-dose (HD) melphalan, 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 4º C for 24 to 48 hours instead of cryopreserving them. Then the fresh stem cells were infused within 24 hours after administration of HD melphan.

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 tandem transplant 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 alive 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. Time periods of autologous HSCT (2010- 2017 versus 2018-2022) and type of autologous HSCT (inpatient or outpatient basis), were evaluated as factors with potential impact on survival rates (OS and PFS).

**Results**

During the study period, 11 years and 113 days, a total of 135 autologous HSCTs were performed for 119 patients with MM at KFSH in Dammam, Saudi Arabia. Single autologous grafts were offered to 119 patients. Twelve of these 119 patients received planned tandem autologous HSCTs while four other patients received second autologous grafts due to relapse or progression of their MM after receiving appropriate salvage therapies. Out of the 119 patients, there were 61 females and 58 males and the median age of patients at HSCT was 51.5 years. At the presentation of their myeloma, the following HR features were encountered: stage III disease according to the RISS in 12.3% of patients, adverse...
cytogenetics in 31.93% and extensive bone involvement in 60.50% of patients, while 11.76% of patients had either renal dysfunction or end-stage renal disease (ESRD) (Tables 1-4). Out of the 135 autologous HSCTs, 104 autologous HSCTs (77.04%) were performed using non-cryopreserved stem cells while 31 autologous grafts (22.96%) used cryopreserved stem cells. Additionally, 54 autologous HSCTs (40.00%) were performed at the outpatient setting while 81 autografts (60.00%) were conducted inpatient. Out of the 54 autologous HSCTs that were performed at outpatient: in 39 transplants (72.22%) fresh or non-cryopreserved stem cells were used, while in 15 autologous HSCTs (27.78%) cryopreserved stem cells were used.

Regarding the initial therapy administered to the primary disease, 89.9% of our patients received bortezomib-based therapy either the doublet regimen bortezomib and dexamethasone (VD) or a triplet regimen such as V Rd and only 9% of patients (7.6%) received more intensive regimens containing PACE chemotherapy (cisplatin, doxorubicin, cyclophosphamide and etoposide) including VTD-PACE, V Rd-PACE and KRd-PACE (Table 5). The number of lines of chemotherapy administered before autologous HSCT was as follows: 88 patients (73.9%) received 1 line of therapy, 20 patients (16.8%) received 2 lines of therapy, while 11 patients (9.2%) received ≥ 3 lines of chemotherapy (Table 6). Thirteen patients (9.6%) achieved partial response (PR), 82 MM patients (60.3%) achieved very good PR (VGPR), and 39 patients (28.7%) achieved complete response (CR) while only 2 MM patients (1.5%) achieved stringent CR prior to autologous HSCT (Table 7). Twenty-seven patients (22.7%) received maintenance therapy for 1 to 2 years, 63 patients (52.9%) received maintenance treatment till disease progression, and 29 patients (24.4%) did not receive maintenance therapy (Table 8).

Survival at day 100 post-HSCT for all patients with MM

Table 1: Stage of disease in patients with MM according to the revised international staging system (RISS) subjected to Auto-HSCT.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>52</td>
<td>43.7</td>
</tr>
<tr>
<td>II</td>
<td>41</td>
<td>34.5</td>
</tr>
<tr>
<td>III</td>
<td>22</td>
<td>12.3</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>3.7</td>
</tr>
</tbody>
</table>

MM: Multiple Myeloma; Auto-HSCT: Autologous Hematopoietic Stem Cell Transplantation.

Table 2: Cytogenetic abnormalities in patients with MM subjected to Auto-HSCT.

<table>
<thead>
<tr>
<th>Cytogenetic abnormality</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>38</td>
<td>31.93</td>
</tr>
<tr>
<td>Chromosome 3 abnormalities including deletion of chromosome 3</td>
<td>12</td>
<td>10.08</td>
</tr>
<tr>
<td>17 p Deletion</td>
<td>10</td>
<td>8.40</td>
</tr>
<tr>
<td>Translocation of chromosome 14 including: t (4;14); t (6;14); t (14;16); t (14;20)</td>
<td>19</td>
<td>15.97</td>
</tr>
<tr>
<td>Trisomies of chromosomes: 3, 7, 9, 15, 17</td>
<td>15</td>
<td>12.60</td>
</tr>
<tr>
<td>Monosomies of chromosomes: 13, 16</td>
<td>9</td>
<td>7.56</td>
</tr>
<tr>
<td>Not available; Unknown</td>
<td>16</td>
<td>13.45%</td>
</tr>
</tbody>
</table>

MM: Multiple Myeloma; Auto-HSCT: Autologous Hematopoietic Stem Cell Transplantation.

Table 3: Bone lesions in patients with MM subjected to Auto-HSCT.

<table>
<thead>
<tr>
<th>Type of Bone Involvement</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized or single lytic lesion (s)</td>
<td>20</td>
<td>16.8</td>
</tr>
<tr>
<td>Multiple lytic lesions</td>
<td>60</td>
<td>50.42</td>
</tr>
<tr>
<td>Pathological fractures requiring surgery</td>
<td>12</td>
<td>10.08</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>43</td>
<td>36.13</td>
</tr>
</tbody>
</table>

MM: Multiple Myeloma; Auto-HSCT: Autologous Hematopoietic Stem Cell Transplantation.

Table 4: Renal dysfunction in patients with MM subjected to Auto-HSCT.

<table>
<thead>
<tr>
<th>Type of renal dysfunction</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>End stage renal disease (ESRD) on hemodialysis [serum creatinine: 629 - 1328]</td>
<td>4</td>
<td>3.36</td>
</tr>
<tr>
<td>ESRD not yet on hemodialysis [serum creatinine: 381 - 477]</td>
<td>2</td>
<td>1.68</td>
</tr>
<tr>
<td>Creatinine clearance &lt; 10</td>
<td>8</td>
<td>6.72</td>
</tr>
</tbody>
</table>

MM: Multiple Myeloma; Auto-HSCT: Autologous Hematopoietic Stem Cell Transplantation.

Table 5: Initial therapy given to patients with MM subjected to Auto-HSCT.

<table>
<thead>
<tr>
<th>Regimen/Protocol</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib + Dexamethasone [VD]</td>
<td>21</td>
<td>17.6</td>
</tr>
<tr>
<td>Bortezomib triplet protocols VTD/VCD/V Rd</td>
<td>86</td>
<td>72.3</td>
</tr>
<tr>
<td>Lenalidomide + dexamethasone [RD]</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>More intensive regimens VTD-PACE / VRd-PACE / KRd-PACE</td>
<td>9</td>
<td>7.6</td>
</tr>
</tbody>
</table>

MM: Multiple Myeloma; Auto-HSCT: Autologous Hematopoietic Stem Cell Transplantation.

Table 6: Number of lines of therapy given to patients with MM prior to Auto-HSCT.

<table>
<thead>
<tr>
<th>Number of treatment lines</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>88</td>
<td>73.9</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>16.8</td>
</tr>
<tr>
<td>≥ 3</td>
<td>11</td>
<td>9.2</td>
</tr>
</tbody>
</table>

MM: Multiple Myeloma; Auto-HSCT: Autologous Hematopoietic Stem Cell Transplantation.

Table 7: Treatment responses achieved in patients with MM prior to Auto-HSCT.

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response [PR]</td>
<td>13</td>
<td>9.6</td>
</tr>
<tr>
<td>Very good partial response [VGPR]</td>
<td>82</td>
<td>60.3</td>
</tr>
<tr>
<td>Complete response [CR]</td>
<td>39</td>
<td>28.7</td>
</tr>
<tr>
<td>Stringent complete response [str. CR]</td>
<td>2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

MM: Multiple Myeloma; Auto-HSCT: Autologous Hematopoietic Stem Cell Transplantation.

Table 8: Maintenance therapy administered to patients with MM subjected to Auto-HSCT.

<table>
<thead>
<tr>
<th>Given/Not given/Duration</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given for 1-2 years</td>
<td>27</td>
<td>22.7</td>
</tr>
<tr>
<td>Given till disease progression</td>
<td>63</td>
<td>52.9</td>
</tr>
<tr>
<td>Not given</td>
<td>29</td>
<td>24.4</td>
</tr>
</tbody>
</table>

MM: Multiple Myeloma; Auto-HSCT: Autologous Hematopoietic Stem Cell Transplantation.

who received their autologous HSCTs including those who received their autologous grafts at outpatient was 100%. The median time for neutrophil engraftment with granulocyte-colony stimulating factor (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. The

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https://www.stemcelltherjournal.com/
main complications encountered in the early post-transplant period were as follows: mucositis (grades I to III) in 38% of patients, engraftment syndrome (ES) in 24% of patients, while episodes of febrile neutropenia (FN) were encountered in 31% of patients. The manifestations of ES were: fever, green watery diarrhea, and rarely skin eruptions. The main risk factors for ES were: heavily pre-treated patients with MM, second autologous HSCTs and > 6.0 x 10^6 CD34 + cells/kilogram body weight. However, severe forms of ES developed in 2 heavily pre-treated HR patients. The first patient had capillary leak syndrome while the second patient developed cytomegalovirus colitis. Despite the complications, both patients were treated successfully.

The long-term outcomes of our patients were excellent. The 4-year OS and PFS for all patients with MM who received their autologous grafts during the study period were 76% and 60% respectively (Figure 1). The 4-year OS and PFS for patients with MM who received non-cryopreserved stem cells, that is fresh grafts, over the same period of time were 82% and 68% respectively (Figure 2). However, there were no significant differences in PFS or OS between patients with MM who received their autografts as an inpatient or as an outpatient (Figures 3,4). Although the 5-year PFS for patients with MM transplanted between 2010 and 2017 was higher than PFS for patients transplanted between 2018 and 2022, the difference was not statistically significant (Figure 5). However, the 5-year OS for patients with MM transplanted between 2010 and 2017 compared to those patients transplanted between 2018 and 2022 showed a difference that was highly significant (Figure 6).

**Discussion**

Since the mid-1990s and despite the recent availability of several lines of novel agents, HD melphalan followed by autologous HSCT is still the standard of care for newly diagnosed patients with MM who are eligible for autologous HSCT [7,12-16]. Eligibility for autologous HSCT is determined by: age, performance status, presence as well as the severity of comorbid medical conditions, and frailty score as frailty has

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**Figure 1:** Overall and progression free survival for all patients autografted for multiple myeloma: 2010-2022.

**Figure 2:** Overall and progression free survival for patients autografted for multiple myeloma with fresh grafts: 2010-2022.

**Figure 3:** Progression free survival for patients autografted for multiple myeloma by in-or out-patient basis: 2010-2022.

**Figure 4:** Overall survival for patients autografted for multiple myeloma by in-or out-patient basis: 2010-2022.

**Figure 5:** Progression free survival for patients autografted for multiple myeloma by the year of transplant: 2010-2017 versus 2018-2022.
been shown to be a predictor of short survival and is considered an exclusion criterion for autologous HSCT [7,15,17,18]. The long-term outcome of patients with MM subjected to autologous HSCT has improved significantly over the last 3 decades [8,19]. Nishimura KK et al reported the long-term outcomes of a total of 4329 patients with newly diagnosed MM treated with autologous HSCT using cryopreserved stem cells at the University of Arkansas in the USA between 1989 and 2014 [19]. The 5 years PFS for the entire population of autologous HSCT recipients had improved from 29% to 68% and the OS for the entire population of autologous HSCT recipients had improved over that time period from 47% to 70% respectively [19]. Cryopreservation of hematopoietic stem cells is routinely employed in the setting of autologous HSCT [3,7,20]. The standard conditioning regimen for patients with MM undergoing autologous HSCT is HD melphalan (200 mg/m²) given intravenously [3,5,7,12,14,15]. However, in patients with renal dysfunction or failure, dose reductions to 100-140 mg/m² may be needed according to creatinine clearance [5,7]. In patients with MM having renal impairment, several studies have shown that: (1) conditioning therapy with melphalan 140 mg/m² has an acceptable toxicity and is equally effective to melphalan dose of 200 mg/m² and (2) melphalan dose adjustment is not indicated in patients having renal failure subjected to autologous HSCT [21-28]. In patients with MM having ESRD receiving hemodialysis, careful evaluation prior to autologous HSCT with the involvement of a multidisciplinary team should be made and dose adjustment for all drugs that adversely affect renal function should be taken into consideration [29,30]. In our study, we did not exclude patients with MM having severe renal dysfunction or even ESRD from having autologous HSCT. Six patients with MM had ESRD, 4 of them were receiving regular hemodialysis and 8 more patients having severe renal dysfunction received their autologous HSCT at our institution. The main differences in the management of these patients compared to those patients with MM having normal renal function were: modifying the doses of medications such as chemotherapy including melphalan conditioning and novel agents according to creatinine clearance. Also, these medications were administered and stem cells were infused after hemodialysis. Melphalan is cleared from plasma and urine in 1 and 6 hours, respectively. Hence, stem cells can be safely infused as early as 8-24 hours following melphalan administration [3,31]. Additionally, studies have indicated that: peripheral blood stem cells can be stored safely at 4°C for at least 5 days, while the patient receives HD chemotherapy; and the viability of stem cells decreases progressively from day 5 onwards [3,32]. Several old and recent studies in addition to one systematic review have shown that autologous HSCT using non-cryopreserved stem cells is simple, safe, cost-effective and leads to short-term as well as long-term outcomes that are at least equivalent to autologous HSCT using cryopreserved stem cells [3,7,20,31,33-37]. The median times of engraftment following non-cryopreserved autografts were 9-14 days for neutrophils and 13-25 days for platelets [3,31,34]. Additionally, treatment-related mortality (TRM) at day 100 post-HSCT using non- cryopreserved autologous stem cells has ranged between 0.0% and 3.4% [34,37]. In our study, we predominantly used fresh or non-cryopreserved autologous grafts particularly for the first autologous HSCTs even after acquiring cryopreservation facilities. The median times for neutrophil engraftment and platelet engraftment after autologous HSCT were 11 and 17 days respectively. Additionally, TRM at day 100 post-autologous HSCT for all our MM patients who received their autologous transplants at inpatient or outpatient settings was 0.00%.

Studies have shown that HSCT without cryopreservation has the following advantages: allowing autologous HSCT to be performed entirely as outpatient due to the simplicity of its implementation, decreasing transplantation costs and the time between the last induction therapy and HD chemotherapy, prevention of toxicity of DMSO, no significant loss of viability of stem cells provided an infusion of the collected stem cells is made within 5 days of apheresis, expansion of the number of medical institutions performing HSCT and autologous graft versus host disease (GVHD) as well as potent ES [3,31,34-39]. However, HSCT without cryopreservation has the following disadvantages: plenty of coordination is needed between various teams regarding the timing of stem cell mobilization, apheresis, administration of conditioning therapy and infusion of stem cells; limitation of the use of standard HD chemotherapy schedules such as BEAM (BCNU, etoposide, cytarabine and melphalan) employed in the autologous HSCT for patients with lymphoma and inability to store part of the collection and reserving it for a second autologous HSCT in case a rich apheresis product is obtained [3,31,34,37].

In the 1990s and in an era where conventional chemotherapy was the only available treatment, the concept of up-front treatment with a tandem autologous HSCT was attempted to improve PFS and OS [40,41]. Updated results of the EMN02/HO95 trial concluded that double frontline autologous HSCT was superior to single autologous HSCT in terms of PFS and OS in all patients, particularly those having poor prognosis or HR subgroups of patients [42,43]. Tandem autologous HSCT has also been shown to overcome
the expected poor outcome in patients with newly diagnosed MM having HR cytogenetics and extramedullary disease [44]. As compared with a single autologous HSCT, tandem transplantation improves OS among patients with myeloma, especially those who do not have a VGPR after undergoing the first transplantation [45]. In our study, HR-MM patients were planned for tandem autologous HSCTs but only patients who show favorable responses to the first autologous HSCTs were offered tandem transplants. Consequently, twelve of our HR-MM patients received tandem autografts.

Patients with MM are ideal candidates for outpatient autologous HSCT due to the ease of administration of HD melphalan, the relatively low extra-hematological toxicity, and the brief period of neutropenia [46-48]. There are specific inclusion criteria for outpatient HSCT and these include: (1) availability of full-time caregiver; (2) residence within 30 minutes drive from the hospital; (3) favorable comorbidity profile and performance status; (4) stable psychology and expected compliance; and (5) patient preference as well as a signed written consent [47,49-53]. On the other hand, the following criteria exclude patients from outpatient HSCT: (1) age more than 65 years; (2) performance status >1; (3) advanced comorbid medical conditions and severe impairment of organ functions; (4) severe recent infection or colonization with multidrug-resistant micro-organisms; (5) lack of caregiver as well as living > 1-hour drive distance from the hospital; and (6) advanced MM [49,54-56]. Occasionally, recipients of outpatient autologous need hospital admission for ≥1 of the following indications: (1) FN, pneumonia, sepsis, or arrhythmia; (2) severe mucositis and poor oral intake; and (3) declining performance status of the patient to the extent that the family or the caregiver become unable to cope [54,56-61]. In our study, 54 patients (40.00%) received their autologous transplants in an outpatient setting thus saving beds and reducing transplantation costs. We applied the inclusion and exclusion criteria outlined above for considering patients to have autologous HSCT at outpatient. Less than 30% of recipients of outpatient autologous HSCTs required admission for complications such as FN, sepsis, severe mucositis and ES. However, the median time for hospitalization post-HSCT was 3 days.

During the neutrophilic recovery following HSCT, a constellation of clinical manifestations referred to as ES may occur and these include: fever, erythematous skin rash, nausea, vomiting, diarrhea and noncardiogenic pulmonary edema [38,62]. Early recognition of ES is vital in order to administer appropriate GVHD therapy which includes HD corticosteroids, alemtuzumab, infliximab, daclizumab, and etanercept [38,62-66]. The incidence of ES in our study patients was 24%. Nevertheless, all patients who developed ES including the 2 complicated cases were managed successfully.

In patients with MM, maintenance therapy after autologous HSCT has been shown to deepen and prolong responses and increase OS and PFS [67,68]. The use of lenalidomide maintenance treatment after autologous HSCT in patients with MM had been investigated in 4 phase III randomized control studies which demonstrated a benefit in PFS [69-71]. 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 OS, PFS and event-free survival [68,70,72-75]. Bortezomib alone or in combination with other drugs such as dexamethasone, thalidomide, and pomalidomide has been shown to be safe, well tolerated, and efficacious in maintenance therapy following autologous HSCT particularly in patients with: HR cytogenetics including deletion 17p; renal insufficiency; previous history of another cancer; and inability to tolerate lenalidomide therapy [75-78]. Continuous therapy has become a key strategy in patients with MM as it has been shown to prolong the duration of remission and significantly improve OS and PFS [79-82]. Currently, continuous therapy till disease progression represents the standard approach for patients with MM both at diagnosis and at relapse as it provides better disease control [83]. Risk-adapted therapy is recommended as patients having HR-MM may benefit from more intensive maintenance treatment than patients with SR-MM [81]. Maintenance therapy was given to 52.9% of our MM patients. Surprisingly, the OS of patients with MM who received their autologous grafts between 2018 and 2022 and who received continuous therapy was significantly lower than that for patients who received their autografts between 2010 and 2017 and who received maintenance therapy for 1 to 2 years.

Despite including a relatively large number of patients in our study that extended over more than 11 years, we acknowledge that retrospective studies have their own limitations. Also, we are eager to know whether the findings reported in Figures 5 and 6 are reproduced by other studies.

Conclusion

Our patients developed MM at a much younger age than in western countries. Additionally, significant proportions of our patients presented with HR features such as advanced RISS stage, adverse cytogenetics and advanced bone disease. Autologous HSCT without cryopreservation 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 autologous transplantation with cryopreservation. Even after having cryopreservation facilities installed at our institution about 10 years ago, the excellent outcomes encountered encouraged us to continue offering fresh cells for the first autografts given to patients with MM. Fresh autologous grafts allowed us to perform 40% of autologous transplant procedures in outpatient settings in order to save beds and reduce costs. MM patients having severe renal dysfunction...
and even ESRD should not be excluded from autologous HSCT as they can benefit from autologous HSCT provided enough attention is given to the drug dose adjustment and timing of administering drugs in relation to hemodialysis.

**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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