Chapter

An Update on Hematopoietic Stem Cell Transplantation in Patients with Multiple Myeloma

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Abstract

Over the past two decades, treatment of multiple myeloma (MM) has advanced dramatically. However, despite the introduction of several lines of novel therapeutics, autologous hematopoietic stem cell transplantation (HSCT) followed by maintenance therapy is the current standard of care in transplant eligible patients. Autologous HSCT can be performed with or without cryopreservation with equivalent short-term and long-term outcomes. In patients with MM, performance of autologous HSCT at outpatient setting is safe, feasible and has a number of advantages such as saving hospital beds and reducing treatment costs. Autologous HSCT can be safely performed in patients with MM having renal dysfunction or failure although particular attention should be made to the timing of administering medications and stem cells with respect to hemodialysis and dose reduction of specific medications according to creatinine clearance. Tandem autologous HSCT is of value in younger patients with adverse cytogenetics and extramedullary disease. Allogeneic HSCT is the only potentially curative therapeutic modality in MM, but it can only be performed in a small fraction of highly selected patients due to the relatively high treatment-related morbidity and mortality. Despite its valuable role in the treatment of MM, autologous HSCT has its own short-term as well as long-term complications.

Keywords: multiple myeloma, hematopietic stem cell transplantation, cryopreservation, maintenance therapy

1. Introduction

MM accounts for 1% of all cancers and 10–15% of all hematologic malignancies [1, 2]. It 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 [1–4]. The 5 years survival not only in the USA but also globally has more than doubled over the past decades due to the availability of several lines of novel therapeutic agents, HSCT, advancements in diagnostic techniques, and general improvement in health care [4–6]. The diagnostic criteria for multiple myeloma (MM) and staging of the disease according to the revised international staging system (RISS) are shown in **Tables 1** and **2**, respectively [1, 2, 4].

1.	≥ 10% clonal bone marrow (BM) plasma cells or a biopsy-proven plasmacytoma and
2.	Evidence of one or more multiple myeloma-defining events namely: a. CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features felt related to the plasma cell disorder b. BM clonal plasmacytosis ≥60% c. Serum involved/uninvolved free light chain ratio (FLC) ≥ 100 (provided that involved FLC is ≥100 mg/L) d. More than one focal lesion on magnetic resonance imaging

Table 1.
Diagnostic criteria for multiple myeloma.

Stage I	All of the following: a. Serum albumin ≥3.5 g/ dL b. Serum beta 2 microglobulin (B2M) < 3.5 mg/L c. Normal serum lactic dehydrogenase (LDH) d. No high-risk cytogenetic abnormalities.
Stage II	a. Not fitting stages I and III. b. Serum B2M: 3.5–5.5 mg/L.
Stage III	All of the following: a. Serum B2M > 5.5 mg/L b. High-risk cytogenetic abnormalities or elevated serum LDH level

Table 2.
Staging of multiple myeloma according to the revised international staging system (RISS).

Presence of the following cytogenetic and molecular abnormalities: del(17p), t(4;14), t(14;16), t(14;20), gain 1q, or p53 mutation implies high-risk (HR) MM. Additionally, the presence of any two HR factors is considered double-hit myeloma; three or more HR factors are triple-hit MM [1].

The treatment of MM has advanced dramatically in the past two decades [7]. Induction therapy with a proteasome inhibitor, an immunomodulatory agent, and dexamethasone followed by autologous hematopoietic stem cell transplantation (HSCT), and maintenance therapy with lenalidomide are among the treatments that are considered the standard care for standard risk (SR) and eligible patients [8, 9]. The triplet regimen of bortezomib, lenalidomide, and dexamethasone (VRd) is recommended as the standard first-line treatment, although the addition of a fourth drug can improve efficacy and survival. In transplant-eligible patients, 3–4 cycles of VRd induction therapy can be administered prior to HSCT while in HR patients, daratumumab, bortezomib, lenalidomide, dexamethasone (Dara-VRd) is an alternative to VRd [1, 10–14]. Selected SR patients can receive additional cycles of induction, and delay in transplant until the first relapse [1]. After autologous HSCT, SR patients need lenalidomide maintenance, while bortezomib-based maintenance is needed for patients with HR myeloma [15, 16]. The role of a 4-drug induction regimen is still being defined but can be considered for patients with HR disease [1, 7, 10, 12]. For patients who are eligible to undergo HSCT, this option is of value in case the transplant

is delayed or refused by the patient [8]. Patients who are not candidates for transplant are typically treated with VRd, for approximately 8–12 cycles followed by lenalidomide maintenance. Alternatively, these patients can be treated with the triplet regimen: daratumumab, lenalidomide, dexamethasone (DRd), or the quadruplet regimen: daratumumab, bortezomib, melphalan, and prednisolone (D-VMP) [1, 17–19].

Unfortunately, nearly all MM patients ultimately relapse, even those who experience a complete response (CR) to initial therapy [2]. In patients with relapsed disease, it is important to switch treatment to new drug classes; for this, multiple combinations can be recommended [8]. Management of the relapsed disease remains a critical aspect of MM care and an important area of ongoing research [2]. In case of refractory disease, most patients require a triplet regimen at relapse, with the choice of regimen varying with each successive relapse [1]. The updated National Comprehensive Cancer Network (NCCN) guidelines include new drugs for refractory disease such as selinexor and belantamab mafodotin which are listed as other regimens [8]. For relapsed/refractory myeloma (RRMM) patients, novel agents such as selinexor and venetoclax are superior to bortezomib. Also, chimeric antigen receptor (CAR)-T cells and other cell-surface-targeted therapies appear promising [7].

2. Autologous HSCT in patients with MM

Since the mid-1990s and despite the recent availability of several lines of novel agents, high-dose (HD) melphalan followed by autologous HSCT is still the standard of care for newly diagnosed patients with MM who are eligible for autologous HSCT [20–23]. The long-term outcome of patients with MM subjected to autologous HSCT has improved significantly over the last three decades [1, 24]. 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 [24]. The 5 years progression-free survival (PFS) for the entire population of autologous HSCT recipients had improved from 29–68% and the overall survival (OS) for the entire population of autologous HSCT recipients had improved over that period of time from 47–70%, respectively [24]. Eligibility for autologous HSCT is determined by 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 [25–27]. Cryopreservation of hematopoietic stem cells is routinely employed in the setting of autologous HSCT [23].

Melphalan is the standard chemotherapeutic agent that is used in conditioning therapy prior to autologous HSCT in MM [20, 23]. According to creatinine clearance, the dose ranges between 140 and 200 mg/m^2, and the drug is administered intravenously (IV) [23, 28, 29]. However, large interpatient variability in melphalan exposure exists among MM patients undergoing autologous HSCT. Additionally, higher melphalan exposure has been shown to improve survival at the expense of increased but acceptable transplant-related toxicities. So, it is recommended to apply pharmacokinetic testing and individualized dosing of melphalan in MM patients undergoing autologous HSCT [30]. In patients with MM having renal impairment, several studies have shown that: (1) conditioning therapy with melphalan 140 mg/m^2 has acceptable toxicity and is equally effective to a melphalan dose of 200 mg/m^2, and (2) melphalan dose adjustment is not needed in patients having renal failure subjected to autologous HSCT [31–38]. However, in patients with MM having renal impairment subjected

to autologous HSCT: (1) it is advisable to reduce the dose of melphalan by 25% in patients having creatinine clearance between 10 and 45 ml/minute and by 15% in patients having creatinine clearance between 46 and 60 ml/min, respectively; and (2) melphalan dose of 200 mg/m^2 is safe and effective in patients having creatinine clearance between 30 and 60 ml/minute [30, 39]. In patients with MM having end-stage renal disease (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 [40, 41].

The doses of granulocyte colony-stimulating factor (G-CSF) and plerixafor; which is used in case of poor mobilization in heavily pretreated patients with MM; in stem cell mobilization prior to autologous HSCT are as follows: (1) G-CSF: 5 μg per kilogram (kg) body weight twice daily subcutaneously (SC) twice daily [ie 10 μg/kg/day] for 4–5 days, and (2) plerixafor: 0.24 mg/kg SC, one dose to be given the night before stem cell collection [42–45]. The doses of cyclophosphamide in stem cell mobilization prior to autologous HSCT are as follows: (1) low dose: 1.0 to 1.5 g/m^2 IV; (2) intermediate dose: 3.0 to 4.0 g/m^2 IV; and (3) high dose: 5.0 to 7.0 g/m^2 IV [23, 46–49].

3. Autologous HSCT without cryopreservation

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 [23, 50]. Since 1957, there have been preclinical data supporting the use of non-cryopreserved HSCs. Also, studies on mice have reported successful rescue after the administration of lethal doses of total body irradiation and reinfusion of BM cells that had been stored for 11 days at 25°C [50]. Studies have shown that: (1) peripheral blood stem cells can be stored safely at 4°C for at least 5 days, while the patient receives HD chemotherapy; and (2) the viability of stem cells decreases progressively from day 5 onwards [23, 51]. Three studies that compared immediate cryopreservation of peripheral blood progenitor cell products and overnight storage showed that there was no statistically significant difference between the two groups regarding: viability of stem cells, neutrophil and platelet engraftment days, safety, and even long-term outcome of the primary disease. Additional benefits of overnight storage of stem cells were a reduction in costs and processing time [52–54].

Several studies and one meta-analysis have shown that non-cryopreserved autologous HSCT for MM is simple, safe, and cost-effective and gives results that are at least equivalent to autologous HSCT with cryopreservation [23, 50, 55]. Treatment-related mortality (TRM) at day 100 post-HSCT using non-cryopreserved autologous stem cells has ranged between 0.0 and 3.4% [28, 55]. Non-cryopreserved stem cells can be infused till day 5 post-apheresis without viability loss provided they are stored at +4°C in a conventional blood bank refrigerator [23, 28, 50]. In a systematic review that included 16 studies having 560 patients with various hematologic malignancies (HMs) including MM, hematopoietic engraftment was universal and only one graft failure was reported [23, 50]. Several old and more recent studies have shown that the median times of engraftment following non-cryopreserved autografts were 9–14 days for neutrophils and 13–25 days for platelets [23, 50, 56–63]. Transplantation of non-cryopreserved stem cells may be of value in two scenarios: (1) use in medical institutions from areas with limited economic resources, that is, having the infrastructure to treat HMs but not cryopreservation facilities, and (2) use in medical institutions

treating HMs and in the process of establishing an HSCT program that will eventually have cryopreservation [28, 50, 55, 64].

HSCT without cryopreservation has several advantages including (1) allowing autologous HSCT to be performed entirely as an outpatient due to the simplicity of its implementation, (2) decreasing transplantation costs and the time between the last induction therapy and HD chemotherapy, (3) prevention of dimethyl sulfoxide toxicity, (4) no significant loss of viability of the collected HSCs provided stem cell infusion is made within 5 days of apheresis, (5) expansion of the number of medical institutions performing stem cell therapies, and (6) potent engraftment syndrome and autologous graft versus host disease (GVHD) [23, 28, 50, 55, 65–68]. HSCT without cryopreservation has the following disadvantages: (1) 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; (2) limitation of the use of standard HD chemotherapy schedules such as BEAM (BCNU, etoposide, cytarabine, and melphalan) employed in the autologous HSCT for lymphoma, and (3) inability to store part of the collection and reserving it for a second autologous HSCT in case a rich product is obtained [23, 28, 50, 55].

4. Autologous HSCT in patients with MM having renal failure

Renal failure is one of the most common and most serious complications of MM that is associated with high mortality [41, 69–72]. Renal impairment has been reported in 30–50% of patients with newly diagnosed MM, while renal failure occurs in 20–30% of MM patients. Additionally, renal impairment develops in 50% of patients with MM during the course of the disease, and approximately 5–10% of MM patients having renal failure at diagnosis are dialysis-dependent [34, 36, 37, 73–75]. Causes of renal dysfunction/failure in patients with MM include: light chain-induced proximal tubular damage, cast nephropathy, interstitial nephritis, dehydration, hypercalcemia, hyperuricemia, amyloid deposition, plasma cell infiltration, hyperviscosity, various infections, nephrotoxic drugs, and contrast media [36, 37, 72, 76]. The modalities of treatment of renal dysfunction/failure in MM patients include: hydration, treatment of infectious complications, withholding nephrotoxic drugs and contrast media, renal replacement therapy such as hemodialysis, removal of serum-free light chains by plasma exchange, use of high cut-off dialyzers, administration of anti-myeloma chemotherapy, HSCT for patients with controlled disease, and renal transplantation [37, 71, 75–77].

In patients with MM having dialysis-dependent renal failure, the use of induction therapy with novel agents and high cut-off dialyzers has resulted in an improvement of renal function due to the removal of large quantities of serum-free light chains [37, 75, 77]. Factors associated with a high probability of dialysis independence in patients with newly diagnosed MM having dialysis-dependent renal failure include: shorter duration of kidney disease, achieving at least very good partial response (VGPR), low beta 2 microglobulin at diagnosis, and low level of free light chains at diagnosis [70]. In patients with MM having renal dysfunction/failure, recovery of renal function depends on: the elimination of causes of renal dysfunction/failure, and timely induction therapy using novel agents such as bortezomib in addition to corticosteroids followed by autologous HSCT once the disease is under control [37, 70, 71, 73, 76]. In patients with MM having dialysis-dependent renal failure, HD chemotherapy and autologous HSCT have traditionally

been contraindicated due to the following reasons: lower survival rates, higher short-term mortality, greater susceptibility to infectious complications, longer duration of hospitalization, greatly compromised quality of life, as well as predilection for the following complications: mucositis, cardiac arrhythmias, bleeding, and encephalopathy [34, 37, 72, 74, 78, 79].

Patients with MM having renal dysfunction and even those having ESRD receiving hemodialysis should not be excluded from autologous HSCT as several studies have proven not only the safety but also the efficacy of HD chemotherapy and autologous HSCT in this group of patients [35, 37, 40, 69, 74, 79–81]. Historically, the fist autologous HSCT performed for a patient with MM having renal insufficiency was reported in the year 1997 [82]. In patients with MM having renal impairment, studies have shown that: (1) induction therapy with almost all the combinations of novel agents such as VRd and bortezomib, cyclophosphamide and dexamethasone (VCD) results in the reversal of renal impairment in the majority of patients, and (2) despite the acceptable toxicity, consolidation with autologous HSCT can overcome the adverse impact of renal impairment on survival and may further improve renal function in at least one-third of patients [34, 37, 83, 84]. Factors associated with a high probability of recovery of renal function in patients having renal failure subjected to autologous HSCT include: being on hemodialysis for less than 6 months, and pre-transplant creatinine clearance >10 ml/minute [71].

In patients with MM having ESRD receiving hemodialysis, careful evaluation prior to 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. In patients with MM having ESRD on hemodialysis, it is recommended to perform hemodialysis before and 24 hours after the administration of HD melphalan [78]. Additionally, in patients with MM having ESRD, combined HSCT and renal transplantation can be performed either simultaneously or sequentially after controlling MM by appropriate chemotherapy [37, 71, 85, 86].

The prognostic factors that imply good prognosis in patients with MM having severe renal impairment subjected to autologous HSCT include: (1) good performance status, (2) higher albumin concentration, (3) chemotherapy-responsive disease in the pre-HSCT period, (4) adjustment of melphalan dose to that of chronic kidney disease, and (5) intensive supportive care post-transplantation [87]. Autologous HSCT is a safe and effective therapeutic modality in patients with ESRD even those on regular hemodialysis [87, 88]. However, patients who demonstrate renal deterioration at one-year post-HSCT should be monitored closely as this predicts poor long-term survival [88]. In patients with MM subjected to autologous HSCT, autologous transplantation does not adversely affect renal function [89]. One study showed that peritoneal dialysis is safe in patients with MM having ESRD subjected to autologous HSCT [90].

In patients with MM having renal impairment, two studies have demonstrated that the use of bortezomib-containing therapeutic regimens in induction treatment as well as in maintenance therapy after autologous HSCT can overcome the negative prognostic impact of renal impairment in this group of patients [91, 92]. However, two other studies have shown the superiority of carfilzomib-based therapeutic regimens as compared to bortezomib-based treatment not only in improving renal function but also in offering better survival outcomes in patients with RRMM having various degrees of renal impairment [93, 94]. Novel agents have helped to widen the treatment options that are available for patients with renal impairment and RRMM, since dose adjustments are unnecessary with dexamethasone, bortezomib, carfilzomib, panobinostat, elotuzumab, pomalidomide, or daratumumab in patients with renal impairment [39, 95]. Pretransplant hemoglobin level and creatinine clearance represent important determinants of clinical

outcomes after autologous HSCT conditioned with melphalan dose of 200 mg/m^2. Patients having lower hemoglobin levels and creatinine clearance were reported to achieve longer treatment-free survival despite experiencing increased toxicity, likely due to higher melphalan exposure [96]. Finally, studies have shown that despite the requirement of hemodialysis at the time of autologous HSCT, patients with MM having ESRD may recover their renal function at least partially [97, 98]. So, in patients with MM having ESRD, it is recommended to perform autologous HSCT as early as possible [98].

5. Tandem autologous HSCT in MM

In the 1990s and in an era where conventional chemotherapy was the only available drug, the concept of up-front treatment with a tandem autologous HSCT was attempted to improve PFS and OS [99, 100]. Previous randomized trials had demonstrated improved outcomes with tandem transplantation in terms of PFS and OS even in patients who had not achieved a VGPR after the first transplant [20, 100].

In the era of novel drugs, clinical trials such as EMN02/HO 95 and StaMINA are needed to evaluate the impact of tandem transplantation [101, 102]. Although the results have to be interpreted with caution due to high drop-out rates, lack of use of novel therapy, and lack of subgroup analysis, the long-term analysis of the GMMG-HD2 trial that compared single versus tandem transplantation with conditioning with melphalan (200 mg/m^2) showed non-inferiority of single transplantation compared to tandem in the sense that OS and EFS did not significantly differ and that the CR rates were significantly improved after the second transplantation [103]. The EMN02/HO95 trial which explored the result of tandem versus single transplantation in newly diagnosed MM patients showed that tandem transplantation improved the depth of the response by 25% with more than 50% of the patients achieving at least a CR and that PFS and OS were significantly improved after a second transplant, with approximately 30% reduction in the risk of death and progression [102]. Updated results of the EMN02/HO95 confirmed the improved 3-year PFS in tandem autologous HSCTs and showed the positive effect of tandem autologous HSCT in HR groups [102, 104]. So, the analysis concluded that double frontline autologous HSCT was superior to single autologous HSCT in terms of PFS and OS in all patients, particularly poor prognosis subgroups of patients [102, 104]. However, the StaMINA trial failed to show the superiority of tandem versus single transplant in the era of novel agents although more than 30% of patients randomized to tandem transplant did not receive the second transplant [101]. Overall, with the currently available data, a second autologous HSCT may be beneficial in HR patients including patients with adverse cytogenetics and RISS stage III disease [20].

In patients with newly diagnosed MM having HR cytogenetics and extramedullary disease, tandem autologous HSCT has been shown to overcome the expected poor outcome [105]. As compared with a single autologous HSCT after HD chemotherapy, tandem transplantation improves OS among patients with myeloma, especially those who do not have a VGPR after undergoing the first transplantation [106]. In comparison with a single autologous HSCT as up-front therapy for newly diagnosed MM, double autologous HSCT achieved superior CR or near CR (nCR) rate, relapse-free survival (RFS), and event-free survival (EFS), but failed to significantly prolong OS. Benefits offered by double autologous HSCT were particularly evident among patients who failed to achieve at least nCR after one auto-transplantation [107]. Whether tandem autologous transplantation will continue to provide benefits in this

HR population with an extramedullary disease in an era of highly active induction regimens, cellular therapeutics, and effective maintenance therapy is an open question, but Gagelmann and colleagues have provided evidence that outcomes with a tandem transplant are superior to standard induction and a single transplant alone and should be weighed as an option taking into consideration the following factors: patient and disease characteristics, trial availability, and access to active triplet and quadruplet induction regimens [108]. A tandem autologous HSCT approach should be considered for all patients, although the benefit from the second autologous HSCT in patients who are in CR or experience a VGPR should be answered in a clinical trial. Recent results with the new induction regimens indicate that there is a role for tandem autologous HSCT in the presence of adverse cytogenetic abnormalities [109].

Tandem HSCT; with autologous HSCT followed by non-myeloablative allogeneic HSCT; is an effective therapy for HR or relapsed MM [110]. Planned allogeneic HSCT after autologous HSCT has not been found to be superior in the majority of studies and is not recommended outside a clinical trial. However, single or tandem autologous HSCT are both appropriate options and participation in prospective clinical trials should be encouraged to resolve the debate in the era of novel agents for MM [109]. After a median follow-up of more than 11 years, the prospective, randomized phase III trial (GMMG-HD2) that aimed to demonstrate non-inferiority of single versus tandem HD melphalan followed by autologous transplantation with regard to 2-year EFS in newly-diagnosed MM and which included 358 evaluable patients showed that HD melphalan followed by single autologous HSCT was non-inferior to tandem transplantation in newly diagnosed patients with MM [103].

In a phase II trial that evaluated, for the first time, the safety and efficacy of bendamustine plus HD melphalan as a conditioning regimen before the second autologous HSCT in previously untreated MM patients, it was shown that bendamustine plus HD melphalan is feasible as conditioning regimen for second autologous HSCT in MM patients [111]. In a study exploring the safety and efficacy of combining dose-intensified bendamustine (200 mg/m^2 on days −4/−3) with HD melphalan (100 mg/m^2 on days −2/−1) before a second (tandem) autologous HSCT in adverse risk MM patients after the first HD melphalan and autologous HSCT, dose-intensified bendamustine with melphalan conditioning was shown to be safe [112]. Additionally, thiotepa/melphalan is another feasible and safe conditioning regimen for autologous HSCT in MM and should be explored for efficacy in a phase III study [111, 113].

A systematic review and a meta-analysis that included all phase 3 randomized clinical trials evaluating the role of HD therapy followed by autologous HSCT showed that: (1) both HD therapy followed by tandem autologous HSCT and HD therapy followed by single autologous HSCT plus bortezomib, lenalidomide, and dexamethasone were superior to HD therapy followed by single autologous HSCT alone and standard-dose therapy (SDT) for PFS, and (2) for PFS, HD therapy followed by tandem autologous HSCT had the most favorable hazard ratio followed by HD therapy and single autologous HSCT plus bortezomib, lenalidomide, and dexamethasone [114].

However, in the era of novel agents; where novel anti-myeloma drugs are used in induction as well as maintenance therapy; the use of novel therapies might decrease the need for a second transplant and tandem transplantation may not improve OS or PFS in either SR MM or HR MM patients compared to a single transplant [115, 116]. Additionally, the alternative treatment approach to tandem autologous HSCT which is the total therapy 3 (TT3) that includes induction, tandem autologous HSCT, consolidation, and maintenance, has allowed one of the best outcomes in terms of CR/nCR, OS, and PFS [117]. Therefore, induction therapy with novel agents followed by single

autologous HCT and maintenance therapy should remain as the standard of care for newly diagnosed MM patients who are transplant eligible [115, 116].

6. Outpatient autologous HSCT in MM

While historically, due to logistic issues and concerns regarding toxicities and infections, most of the autologous HSCTs were performed in inpatient setting, the swift recovery after peripheral autologous HSCT and improvements in supportive care have enabled patients to receive autologous HSCT at outpatient [60, 118]. It has been reported that outpatient autologous HSCT is safe and feasible in patients with: lymphoma, tumors of the central nervous system, and breast cancer [60, 119–121].

Several studies have shown that; with daily outpatient clinical evaluation and intensive supportive care; outpatient autologous HSCT is safe, feasible, and cost-effective and it can lead to excellent short-term as well as long-term outcomes in carefully selected patients with MM and lymphoma [13, 56, 57, 59–61, 122–135]. However, a multidisciplinary approach with close follow-up is required to guarantee a successful outcome of the autologous outpatient HSCT program [59, 122, 123, 131, 136]. 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 short period of neutropenia [56, 135, 137].

The inclusion criteria of outpatient HSCT include: (1) availability of full-time caregiver; (2) residence within 20–30 minutes-drive from the hospital; (3) favorable performance status and comorbidity profile; (4) stable psychology and expected compliance; and (5) patient preference and signed written consent [60, 124, 125, 132, 134, 135]. On the other hand, the exclusion criteria of outpatient HSCT include: (1) age more than 65 years; (2) performance status >1; (3) severe comorbid medical conditions and severe impairment of organ functions; (4) severe recent or incompletely eradicated infection and colonization with multidrug-resistant micro-organisms; (5) lack of caregiver and living >1-hour drive distance from the hospital; and (6) advanced disease such as MM or lymphoma [60, 61, 63, 118].

Indications for admission in recipients of outpatient HSCT include: (1) febrile neutropenia, pneumonia, sepsis, or arrhythmia; (2) severe mucositis and poor oral intake; and (3) declining performance status of the patient and inability of family or caregiver to cope [57, 61, 118, 123, 129, 130, 138]. Between 8% and 84%. of recipients of outpatient autologous HSCT require hospitalization in the first 100 days post-HSCT and the duration of hospitalization ranges between 4 and 9 days [57, 59, 61, 122, 123, 127, 129, 130]. The 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, while the reported transplant-related mortality is ≤1.1% [57, 59, 61, 123, 124, 126, 127, 129, 130, 132, 136]. Outpatient autologous HSCT has the following advantages: (1) significant reduction in costs and saving beds; (2) patient convenience and high patient satisfaction; (3) lower rate of infections; and (4) lower morbidity and TRM [56, 59, 61, 122, 134, 136, 139–141].

7. Allogeneic HSCT in MM

Despite the current advances in the treatment of MM including the introduction of several classes of novel agents, MM remains incurable and eventually most patients develop progressive disease [142–145]. Currently, allogeneic HSCT represents the

only potentially curative therapy for patients with MM [146–149]. In MM patients, allogeneic HSCT exerts its therapeutic efficacy mainly through its graft versus myeloma (GVM) [143, 144, 146]. It is reasonable to consider allogeneic HSCT as the treatment strategy for younger patients with MM having HR disease as several studies have shown that allogeneic HSCT can potentially overcome the adverse prognosis of HR cytogenetics [143, 146–148]. In MM patients, the use of myeloablative conditioning (MAC) in allogeneic HSCT is associated with high treatment-related mortality (TRM) mainly due to the regimen-related toxicities and GVHD which are translated into considerable transplant-related morbidity and mortality while the use of reduced intensity conditioning (RIC) in allogeneic HSCT is associated with high relapse rates [144, 145, 147–149]. Nevertheless, allogeneic HSCT offers a potentially curative option in 10–20% of patients with RR MM [142]. A study performed at MD Andersen Cancer Centre that included 149 patients with MM subjected to allogeneic HSCT [38 MAC; and 110 RIC] showed that predictors of prolonged survival included: chemosensitive disease in the pre-transplant period in addition to the absence of HR cytogenetics [150].To minimize treatment-related toxicity while allowing the GVM effect, some clinical trials have used RIC-allogeneic HSCT as a tandem approach following autologous HSCT, that is, autologous-RIC allogeneic HSCT in patients with MM who are eligible for HSCT [144, 149]. In patients with RR MM, allogeneic HCT with an RIC regimen is associated with acceptable toxicity as well as durable remissions and long-term survival and the use of novel agents as maintenance therapy following RIC-allogeneic HSCT can reduce the rate of relapse and disease progression [142, 145, 149, 151]. Haploidentical HSCT with post-transplant cyclophosphamide is a feasible option in patients with HR-MM eligible for allogeneic HSCT but lacking HLA-identical donors [146]. The use of CD34-selected stem cells in allogeneic HSCT in patients with MM is safe and effective, although the outcome of CD34-selected HSCT is influenced by the following: age of the patient, extramedullary disease, and disease status prior to CD34-selected HSCT [152]. Whole-body imaging is an appropriate and highly recommended diagnostic approach for the detection of prognostically relevant lesions before and after allogeneic HSCT in patients with MM [153]. The utilization of minimal residual disease evaluation prior to allogeneic HSCT could allow the identification of subgroups of patients who are likely to benefit from allogeneic HSCT [154]. Finally, the role of allogeneic HSCT in patients should be complementary to other available therapeutic options such as: monoclonal antibodies, bispecific T-cell engagers (BiTe), and CAR T-cell therapy [149, 154].

8. Complications of autologous HSCT in patients with MM

8.1 Engraftment syndrome and autologous GVHD

During the neutrophilic recovery following HSCT, a constellation of clinical manifestations that include fever, erythematous skin rash, nausea, vomiting, diarrhea, and noncardiogenic pulmonary edema may occur [67, 155]. These clinical features are usually referred to as engraftment syndrome which may be a manifestation of graft versus host reaction. This syndrome reflects cellular and cytokine interactions and may be associated with significant transplant-related mortality and morbidity due to pulmonary leak syndrome and multiorgan failure [155–158]. Early recognition of this syndrome is vital in order to administer appropriate GVHD therapy which includes HD corticosteroids, alemtuzumab, infliximab, daclizumab, and etanercept [67, 155–159].

GVHD is a common complication of allogeneic HSCT [160]. A similar autoimmune syndrome, termed auto-aggregation syndrome or autologous GVHD, has been reported in the setting of autologous HSCT [160, 161]. Autologous GVHD represents the extreme or severe form of engraftment syndrome [68]. The incidence of autologous GVHD is 5–20% [162]. The predisposing factors for autologous GVHD include: MM as the primary disease; second auto-HSCT; heavily pretreated patients; high CD34+ cells infused; HLA B55 expression; low percentages of CD3+ and CD8+ T-cells; and achievement of high levels of absolute lymphocyte counts after HSCT [68, 155–160, 163].

In autologous GVHD, there is dysregulation of the immune responses due to: the primary disease such as MM, HD melphalan used the conditioning therapy before HSCT; and the use of immunomodulatory agents in the treatment of MM [163]. The clinical and histological manifestations of autologous GVHD are similar to those encountered in acute GVHD following allogeneic HSCT although the clinical features tend to be milder and self-limited in most cases [68, 160, 161, 164–166]. Autologous GVHD can involve the: skin, liver, and gastrointestinal tract [68, 160, 162, 164–166]. Treatment is usually symptomatic although immunosuppression with corticosteroids is usually needed in severe cases [68, 160, 164, 162, 165]. Death as a consequence of infectious complications has been reported in severe forms of autologous GVHD [165].

8.2 Other complications of autologous HSCT in MM patients

Autologous HSCT in patients with MM has several complications that can be classified as early or late complications. Early complications occur before day 100 post-HSCT, while late complications are usually encountered after day 100 post-transplantation. The early and late complications are shown in **Table 3** [167–182] and **Table 4** [183–188], respectively. The predisposing factors for the complications of autologous HSCT in patients with MM include: (1) the disease itself; (2) presence of other comorbid medical conditions; (3) old age; (4) renal failure; and (5) drugs used in the treatment of patients with MM such as: corticosteroids, cyclophosphamide, HD melphalan, thalidomide, lenalidomide use before and after HSCT, as well as

1.	Febrile neutropenia
2.	Sepsis; bacteremia with multidrug-resistant organisms
3.	Pneumonia with *Streptococcus pneumoniae*
4.	Cellulitis
5.	Neutropenic colitis
6.	Infections with Candida species
7.	*Clostridium difficile* infections
8.	Oral mucositis
9.	Electrolytic disturbances particularly hypokalemia and hypophosphatemia
10.	Thromboses related to central venous catheters
11.	Acute renal failure
12.	Acute respiratory failure requiring endotracheal intubation and mechanical ventilation

Table 3.
Early complications of autologous hematopoietic stem cell transplantation in patients with multiple myeloma.

(1)	Reactivation of cytomegalovirus and hepatitis-B infections
(2)	Infection with herpes simplex and varicella-zoster viruses
(3)	*Pneumocystis jeroveci* infections
(4)	Infections with Aspergillus species
(5)	Infection with multidrug-resistant organisms
(6)	Therapy-related myelodysplasia and acute myeloid leukemia
(7)	Second primary malignancies such as solid tumors and skin cancer
(8)	Chronic pulmonary complications: lung dysfunction and pneumonitis
(9)	Sexual dysfunction
(10)	Hypothyroidism
(11)	Cataract
(12)	Osteopenia and osteoporosis
(13)	Avascular necrosis of bone
(14)	Hypertension
(15)	Cardiomyopathy and congestive cardiac failure
(16)	Post-traumatic stress disorders: anxiety; and depression

Table 4.
Late complications of autologous hematopoietic stem cell transplantation in patients with multiple myeloma.

bortezomib use before and after autologous transplantation [167, 171–177, 179–185, 187].

9. Maintenance therapy after autologous HSCT in patients with MM

In patients with MM, autologous HSCT has been shown to improve OS and PFS but it is not curative [189]. The residual disease is almost always present after autologous HSCT and is responsible for relapse [190]. Maintenance therapy after autologous HSCT has been shown to deepen and prolong responses and increase OS and PFS [190, 191]. Thalidomide was the first immunomodulatory agent to be used in maintenance therapy after autologous HSCT in MM patients [192, 193]. The use of lenalidomide in the maintenance therapy following autologous HSCT in patients with newly diagnosed MM has been investigated in four phase III randomized control studies [193, 194]. These clinical trials and other studies have shown that lenalidomide maintenance therapy until disease progression prolongs OS, PFS, and EFS in patients with MM [189, 193, 195–197].

In patients with MM, bortezomib induction and maintenance therapy after autologous HSCT improves rates of CR and achieves superior OS and PFS [198]. Bortezomib alone or in combination with other drugs such as dexamethasone, thalidomide, and pomalidomide has been shown to be feasible, well tolerated, and beneficial in maintenance therapy following autologous HSCT in patients with: (1) HR MM such as patients with 17 p deletion; (2) renal insufficiency; (3) previous history of another cancer; and (4) inability to tolerate lenalidomide [16, 199, 200]. However, in patients with newly diagnosed MM lenalidomide maintenance therapy after HD melphalan and autologous HSCT has become the standard of care [190, 193, 196, 199, 201].

10. Continuous therapy after autologous HSCT in MM patients

In younger patients with MM, long-term maintenance therapy after autologous HSCT has been shown to significantly improve OS and PFS compared to observation [202]. Consolidation therapy with VRd regimen followed by lenalidomide maintenance improves PFS and the depth of response in patients with newly diagnosed MM compared to maintenance therapy alone [203]. Compared to the traditional fixed-duration therapy, maintenance therapy approaches in MM offer prolonged disease control and improved outcomes. In patients with newly diagnosed MM, multiple agents have been investigated as long-term options and these include: immunomodulatory agents such as thalidomide and lenalidomide; proteasome inhibitors such as bortezomib, carfizomib, and ixazomib; and monoclonal antibodies such as daratumumab, elotuzumab, and isatuximab [204].

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 [205–207]. Continuous therapy represents the standard approach for patients with MM both at diagnosis and at relapse as it provides better disease control [202]. However, risk-adapted therapy is recommended as patients having HR-MM may benefit from more intensive maintenance treatment than patients with SR-MM [205].

11. Conclusions and future directions

Autologous HSCT followed by maintenance therapy till relapse or disease progression remains the standard of care in patients with MM who are transplant eligible. Autologous HSCT can safely be performed with or without cryopreservation in inpatient or outpatient settings as well as in patients having renal failure. Allogeneic HSCT and tandem autologous HSCT are indicated in a highly selected group of patients with MM particularly younger patients with HR features such as adverse cytogenetics. The recent developments in the treatment of patients with MM include: induction therapy with four drugs; continuous therapy even in transplanted patients; and the use of CAR T-cell therapy, bispecific antibodies, and other novel agents in the treatment of patients having RR-MM. The timing of the incorporation of novel agents, stem cell therapies, and new immunotherapies will be determined by the results of the ongoing clinical trials.

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