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ARTICLE

Autologous stem cell transplantation for multiple myeloma patients aged ≥ 75 treated with novel agents

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Abstract

Autologous stem cell transplantation (ASCT) has been used for treating multiple myeloma (MM) for over three decades and is generally reserved for patients younger than 65. Herein we report on outcomes of outpatient ASCT in a cohort of patients with MM aged ≥75 years. Between October 2005 and August 2020, 50 patients aged ≥75 years, received an ASCT at Mayo Clinic, Rochester. Median time from diagnosis to ASCT was 6.85 months (IQR 5.2–10.52) and 50%. received reduced intensity conditioning with melphalan 140 mg/m^2. 48% of patients completed the ASCT without requiring hospitalization and 52% ($n = 26$) of patients required hospitalization with a median duration of hospital admission of 9 days (IQR 5–13). Reasons for hospitalization included fever or infection (32%), cardiac arrhythmia (36%), and dehydration (32%). Overall response rate was 100% with a complete response seen in 57% of patients. Median overall survival and progression free survival for the cohort were 82 months and 33 months, respectively. One patient died within 100 days of transplant representing a 2% 100-day mortality rate. ASCT is safe and efficacious in carefully selected MM patients aged 75 or above and we believe that age should not be an exclusion factor for ASCT in MM.

Introduction

Over the past two decades, there has been great progress in the treatment of multiple myeloma (MM), with many new medications incorporated into routine treatment [1–4]. Autologous stem cell transplantation (ASCT) has been an integral part of MM treatment for young and for selected fit elderly patients [5, 6] with a proven progression free survival (PFS) benefit [7] and OS advantage [8].

The definition of transplant eligible is ill-defined and different centers have different policies to determine which patients are transplant eligible. Some centers have an age cut-off [9], others use clinical judgment, and some use various frailty scores (a scoring system based on comorbidities and physical and cognitive assessments) aiming to objectively assess transplant eligibility [10, 11].

Age has traditionally been used as one of the variables considered when determining eligibility for ASCT, and some guidelines use arbitrary cut-offs of 65 or 70 years [9, 12]. However, advances in supportive care improved safety of ASCT and lowered transplant related mortality (TRM), suggest that transplant, specifically in older patients, may have a favorable risk benefit ratio. Previous data showed that ASCT is safe in patients over the age of 65 years, with TRM ranging between 1.5–4.5% [13–17]. The beneficial effects of ASCT in younger populations has been studied in a large randomized controlled trial, but these trials usually exclude patients ≥70 years [18, 19].

Elderly patients with myeloma are heterogeneous and in an attempt to individualize treatment, data about the efficacy and safety of ASCT in patient ≥75 years is essential. Herein we report the outcomes of ASCT in a cohort of MM patients 75 years or older.

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Methods

We conducted a retrospective study of all consecutive MM patient aged ≥75 years that underwent ASCT at Mayo Clinic, Rochester, Minnesota. The study was approved by the Mayo Clinic Institutional Review Board (IRB). The diagnosis and staging of MM were according to consensus criteria [20]. For risk stratification, we used the international staging system (ISS) and fluorescence in situ hybridization (FISH) in CD 38 positive sorted plasma cell. High risk FISH was defined according to IMWG risk stratification criteria [21] and included del 17p, t (4;14), t (14;16) and t (14;20).

Our current consensus for eligibility of patients with MM undergoing ASCT are assessed up to 30 days prior to transplant and include: performance status Eastern Cooperative Oncology Group (ECOG) ≤ 2, no significant comorbidities, adequate liver and renal function, respiratory function studies (FEV1 ≥ 50%. DLC ≥ 50%), echocardiography (EF ≥ 40%), chest X-ray, sinus X-ray and a dental evaluation. Plerixafor is used if at day 4 of GCSF injections peripheral CD34+ is less than 10 cells/mcL.

All patients received conditioning consisting of melphalan 140 or 200 mg/m^2. Melphalan doses were decided by the treating physician based on clinical judgment. Melphalan was given as a single day infusion at day -2 with a rest day on day-1 until policy changed in February 2018. From February 2018 till February 2019 melphalan was given as a single day infusion at day -1. After February 2019 policy was changed again (due to evidence of delayed engraftment when melphalan was given at day -1) and patients received melphalan on day -2. Supportive care was provided based on Mayo's standard protocol (including prophylaxis with penicillin, levofloxacin, acyclovir).

Neutrophil engraftment was defined by absolute neutrophil count (ANC) ≥ 500/μl for three consecutive days and platelet engraftment by ≥50000/μl without transfusion support. Bone marrow MRD assessment was carried out using eight color next generation flow cytometry (sensitivity $\geq 1 \times 10^5$).

Response was assessed at day 60 (high risk) to 100 (standard risk) post ASCT according to consensus criteria [22]. Chart review was conducted to assess disease characteristics as well as transplant related outcomes. Data on primary indication for hospitalization and duration of hospitalization were collected on all patients. Continuous variables were described as the median and range of observations. Categorical data were described as the median and interquartile range (IQR).

Transplant related mortality (TRM) was defined as death from any cause within 100 days of stem cell infusion. The median survival time and the probabilities of overall survival (OS) and Progression free survival (PFS) were estimated by the Kaplan-Meier method. OS was defined from day zero of bone marrow transplant to death from any cause. PFS was defined as time from day zero to relapse, assessed by consensus criteria, or time to reinitiating of therapy or death. Cox regression analysis was used to study the association between studied predictors and OS and PFS. Wilcoxon rank sum and chi square tests were used to analyze continues and dichotomous variables, respectively. The two-sided P value <0.05 was considered statistically significant. Statistical analysis was carried out using the JMP 14 (SAS, Cary, NC) statistical software.

Results

Between October 2005 and March 2020, 5870 MM patients were seen at Mayo Clinic, of which 869 where 75-year-old and older. 50/869 (6%) of these underwent an ASCT. Between 2005 and 2020, 2446 MM patients underwent ASCT at Mayo Clinic; 2396 were younger than 75-year-old (2% of transplanted patients at our center were ≥75 years). Baseline characteristics for all 50 patients are listed in Table 1. The median age at day 0 was 76 (range 75–79), patients aged 75–77 accounted for 88% of the cohort. There was a slight male predominance (66%). Ten patients (20%) had high risk cytogenetic features. All patients except one (that was treated with dexamethasone only) received induction with novel agents (listed in Table 1) and 6 patients (12%) received doublet induction. All others received triplet induction.

The median hematopoietic stem cell transplantation specific comorbidity index (HCT-CI) was 0 (range 0–6). It was 0 for 27 patients and 9 patients had HCT-CI of 5 or 6. Transplant related data are summarized in Table 2.

Median time from diagnosis to ASCT was 6.85 months (IQR 5.2–10.52). For peripheral blood progenitor cell collection, granulocyte colony stimulating factors (G-CSF) were used in all patients. Plerixafor was used in 28 patients (56%) with low peripheral CD34+ (<10 cells/mcL). Median time to neutrophil engraftment was 15 days (IQR 13–17) and to platelet engraftment (50000/μl) was 15 days [14–17].

Reduced intensity conditioning (melphalan 140 mg/m^2) was administered to 25 patients (50%). One patient received carfilzomib and melphalan 200 mg/m^2 conditioning as part of a clinical trial. All others (48%) received full dose conditioning (melphalan 200 mg/m^2). Bacteremia was confirmed in 10 patients (2 pseudomonas aeruginosa, 1 acinetobacter, 2 enterococcus faecalis, 2 staph coagulase negative, 1 granulicatella adiacens, 1 elizabethkingia meningoseptica, and 1 staphylococcus epidermidis). There was no association found between melphalan dose and length of hospitalization ($P = 0.155$), chance of achieving

Table 1 Baseline characteristics at diagnosis of study population.

Variable	Cohort $n = 50$
Age at ASCT, median years (IQR)	76 (75–76)
Male, *n* (%)	33 (66)
Median time from diagnosis to ASCT, months (IQR)	6.85 (5.2–10.52).
High risk FISH, *n* (%)	10 (20)
Double hit, *n* (%)	3 (6.5)
Induction treatment, *n* (%)	
VCd/Vd	15 (30)
VRd	26 (52)
KRd/KPd	3 (6)
DPd/DRd/DIRd	4 (8)
Rd/Thal-d	6 (12)
Other (VDTPACE, ICd)	2 (4)
Melphalan conditioning, *n* (%)	
200 mg/m^2	24 (48)
140 mg/m^2	25 (50)
Carfilzomib and melphalan	1 (2)
ISS, *n* (%)	
I	5 (11)
II	12 (26)
III	12 (26)
Missing	17 (37)
Median % bone marrow PC at diagnosis (IQR)	51 (25–78)
Median hemoglobin at diagnosis (IQR), g/dL	10.5 (9–12)
Median serum creatinine at diagnosis (IQR), mg/dL	1 (0.8–1.2)
Median serum albumin at diagnosis (IQR), g/dL	3.4 (3.2–3.5)
Median LDH at diagnosis (IQR), U/L	175 (147–221)
Median M-spike at diagnosis (IQR). g/dL	1.5 (0.1–3)
Response at ASCT, *n* (%)	
CR/sCR	11 (22)
VGPR	24 (48)
PR	10 (20)
SD	1 (2)
PD	3 (6)
Missing	1 (2)
Maintenance treatment, *n* (%)	
VRd/VR	3 (7)
Bortezomib	5 (10)
Lenalidomide	18 (40)
Daratumumab	1 (2.5)
ICd	1 (2.5)
Carfilzomib	1 (2.5)
KRd	1 (2.5)
No maintenance	20 (40)
Best response, *n* (%)	
CR/sCR	26 (52)
VGPR	16 (32)
PR	8 (16)
Pre-transplant regimens, median (range)	1 (1–4)
Relapses pre-transplant, median (range)	0 (0–2)

n number, *PI* proteasome inhibitors, *Imid* immunomodulatory drugs, *CR* complete response, *VGPR* Very good partial response, *PR* partial response, *SD* stable disease, *ASCT* autologous stem cell transplantation, *PC* plasma cells, *VCd* bortezomib, cyclophosphamide, dexamethasone, *Vd* velcade, dexamethasone, *VRd* bortezomib, lenalidomide, dexamethasone, *KRD* carfilzomib, lenalidomide, dexamethasone.

Table 2 Transplant outcomes.

Variable	Cohort $n = 50$
Apheresis collections, median (range)	1 (1–2)
Plexiform use, *n* (%)	28 (56)
CD34 stem cell dose, $\times 10^6$ cells/kg (IQR)	4.9 (3.8–6.1)
Days to neutrophil engraftment, median (IQR)	15 (13–17)
Days to platelets engraftment (50000), median (IQR)	15 (14–16)
Bacteremia, *n* (%)	10 (20)
Hospitalizations, *n* (%)	26 (52)
Infection	9 (32)
Cardiac arrhythmia	9 (36)
Dehydration	8 (32)
Days in hospital of those hospitalized, median (IQR)	9 (5–13)
HCT-CI, median (range)	0 (0–6)

n number, *HCT-CI* hematopoietic stem cell transplantation specific comorbidity index.

sCR MRD negativity ($P > 0.1$), days to neutrophil engraftment ($P = 0.063$), days to platelet engraftment ($P = 0.0914$), and risk of bacteremia ($P = 0.792$).

Stem cell transplantation at our center is routinely performed as an outpatient, with patients being hospitalized when deemed clinically necessary upon physician review. Twenty-four (48%) patients completed the entire course of transplant without hospitalization. Among the 26 patients (52%) that required hospitalization, the median duration of hospital admission was 9 days (IQR 5–13). Reasons for hospitalization included fever or infection (32%), cardiac arrhythmia (36%), and dehydration and need for nutritional support (32%).

Maintenance treatment was used in 29 patients (58%). Lenalidomide was the most common agent used (18 patients). The median follow-up for all surviving patients is 22 months (IQR 11–56). Overall response rate (patients achieving at least a partial response) was 100% with a complete response were seen in 52% of patients. Sixteen patients (52% of patients that underwent MRD assessment)

achieved MRD negative CR. Median OS and PFS for the cohort were 82 months and 33 months, respectively.

Univariable cox regression model that evaluated the effect of gender, high risk cytogenetics, hemoglobin (<10 g/L versus ≥10 g/L), renal function (<60 ml/min/BSA versus ≥60 mg/min/BSA), performance statues, comorbidity index and melphalan dose (140 mg/m^2 vs 200 mg/m^2) did not detect any variable that was predictive of OS or PFS in this highly selected cohort.

One patient had graft failure. The patient was a 76-year-old, received induction treatment that included daratumumab, lenalidomide, ixazomib and dexamethasone and achieved VGPR prior to ASCT. At this point she had an HCT-CI of 6. She received melphalan 200 mg/m^2 at day -2 and received 6.57×10^6 CD34 cells/kg at day 0. There was no finding suggestive of infection as a cause of her graft failure. No improvement was seen with G-CSF, GM-CSF, IVIg, cyclosporine and eltrombopag. In terms of MM she achieved MRD negative sCR. She is alive and transfusion dependent at 8.8 months.

One patient died within 100 days of transplant due to arrythmia, which represented a 2% 100-day mortality (TRM). This patient had an HCT-CI of 6 at pretransplant evaluation. She presented at day 22, after already being discharged, with nausea and vomiting and with negative blood and stool cultures. She was transferred to computerized tomography (CT) scan when she had developed pulseless electrical activity (PEA) and died.

Discussion

ASCT with high dose melphalan remains a cornerstone of treatment in MM. However, there are limited data about outcomes in patients ≥75 years, especially in the outpatient setting. Our data show that ASCT can be safely performed in selected myeloma patients aged 75 or above, with a TRM in our cohort of 2%. 48% of patients completed the ASCT without requiring hospitalization. The overall response rate was 100% with 16 patients achieving MRD negative sCR and a median overall survival was 6.8 years.

The median age at diagnosis in MM is 69 years [23]. Aging is associated with several factors that might increase toxicity: reduced organ function, comorbidities, polypharmacy and reduced drug metabolism. The main concerns about ASCT in the elderly are acute toxicities. Early mortality has been a particular concern when considering an elderly population and, in our cohort, only one patient died before day 100 (at day 22) as a result of a sudden cardiac arrest, resulting in a TRM of 2%. This is comparable to the TRM that was reported in our institution in a cohort of 716 patients with MM (median age 59) receiving ASCT [24]. A retrospective study compared two cohorts: one cohort included 26 patients ages ≥ 65 years that underwent ASCT and the second cohort included 127 patients <65 years that underwent ASCT. There was no difference between the two cohorts in term of hospitalizations, cytopenia, or TRM [25]. In our cohort, age did not have any effect on OS or PFS, and this is in line with previous retrospective data [26]. This could be related to low sample size seeing that, in the large CIBMTR study, age was found to be associated with OS [27], which is reasonable because the expected survival of older patients is shorter. We suspect the selection applied to these patients for eligibility is the primary reason age did not impact outcomes.

The hospitalization rate and nature of complications leading to hospitalization is consistent with what we see in our clinical practice in younger patients with MM receiving ASCT and with previous literature regarding outpatient ASCT [28, 29].

Approximately half of our study population received reduced intensity melphalan a conditioning.

Whilst we generally try and avoid dose reductions [30], in patients aged 75 or above we sometimes use reduced intensity conditioning in an attempt to reduce toxicity. In AL amyloidosis and in MM there is evidence that higher doses of melphalan predict better survival [30, 31]. According to the CIBMTR analysis of patients aged ≥70 years, melphalan dose was predictive of OS and PFS and patients treated with 140 mg/m^2 had lower PFS and OS and higher NRM [27]. In our cohort, melphalan dose was not predictive of OS or PFS, and this may very well be related to small sample size. On the other hand, the superior outcomes for higher doses of melphalan may reflect selection bias (frail patients receive lower doses while fit patients receive full doses). This is supported by the lower NRM in patients that received melphalan 200 mg/m^2. Interestingly, in the CIBMTR report, OS of patients ≥70 years treated with MEL200 was similar to OS in younger patients. Melphalan dose did not significantly affect other outcomes like hospitalization length or engraftment, but this also might be due to small sample size. We do not have documentation of the reasons for dose reductions in most patients, but 19 patients (38%) had HCT-CI score ≥3.

Various scores have been used in an attempt to try to find a more objective and reproducible way to select elderly patients for ASCT [32]. The scores used to evaluate comorbidities in myeloma patients before ASCT are: Hematopoietic cell transplant comorbidity index (HCT-CI), Charlson Comorbidity Index (CCI), revised myeloma comorbidity index (R-MCI) [33], UKMRP [34], Mayo risk score [35] and ancona vulnerability score [36]. R-MCI and UKMRP were recently validated [33, 34]. Frailty score are also used to assess myeloma patients prior to ASCT. IMWG frailty score includes age, deficits in activities of daily living (ADL), impairments in instrumental ADLs (IADL), and the

CCI categorizing patients as fit, intermediate-fit, or frail [10]. In a prospective external validation of the IMWG frailty score [11], 131 patients, ages 65–75, the IMWG frailty score, CCI and HCT-CI were evaluated prior to ASCT, but the decision whether or not to transplant the patient was made independently of those scores. HCT-CI and CCI did not predict different outcomes in transplanted patients, while the IMWG frailty score identified patients ages 70–75 whose outcomes are not improved by ASCT. Another frailty score is the Fried model for frailty, which includes unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. The ability of the IMWG frailty score to predict OS was inferior to Fried model for frailty among patients ≥ 75 years [37] and the authors concluded that using age as a predictor for tolerating ASCT might be inappropriate for fit patients. Frailty and comorbidity scores do not require expensive additional laboratory testing or imaging and are important tools, that can help the treating physician individualize treatment in the elderly. In our study, HCT-CI was 5 or 6 in 8 patients, but sample size is too small to relate to outcomes. Both the patient that died and the one that did not engraft had an HCT-CI of 6.

It is important to understand if similar treatment benefits are observed in the elderly population. There are no randomized studies that compared ASCT to no ASCT in MM patients ≥75 years. Most RCTs that addressed the issue of MM treatment used age as an exclusion criterion [38, 39] and retrospective reports about transplant eligibility also uses age as a cut-off [40] so data are missing about the efficacy of ASCT in this patient population. The efficacy of anti-myeloma therapy in patients ≥ 80 years has been shown in a large study that reported data from the SEER database [41]. Two cohorts were compared, each included over 2000 patients: a cohort of 70–79-year-old MM patients and a cohort of MM patients ages 80 or older (the median age of the latter group was 84 years). Patients in the second cohort that received therapy had better median OS compared to those not receiving therapy (21 months vs 6 months), suggesting that treatment in an older patient is effective. Increasing age is a predictor of worse outcomes to treatment, making ASCT a desired treatment modality. A retrospective study comparing a cohort of 65–70 years old that underwent ASCT to a cohort of the same age that didn't undergo ASCT showed an OS benefit in the transplanted cohort [14].

Our results are similar to the results of a recently published study of 72 patients ages ≥ 75 years [42]. The NRM was 1% and ORR was 91% (29% CR/sCR). Unlike our study, high risk cytogenetics predicted lower OS and PFS. This may be attributed to the higher percent of patients treated with triplets in our study (doublets were given to 13% in our study and 47% in the MDACC study) as well as selection of the fit elderly for transplant. Moreover, in this study, transplants were done as an inpatient, and in our study ASCT is done outpatient and only half of our cohort was hospitalized, demonstrating that the outpatient setting is safe for this population.

According to a large US registry, the improvement in MM outcomes, seen over the last decades, was not seen in patients ≥75 years [43]. The use of ASCT for patients ≥70 years increased in recent years [27]. However, several highly effective treatment options exist for newly diagnosed elderly patients. The MAIA trial compared daratumumab, lenalidomide and dexamethasone (DRd) to lenalidomide and dexamethasone (Rd) in 737 transplant ineligible patients and showed that approximately half the patients treated with DRd achieved CR [44]. The ALCYONE is a phase 3 trial that showed OS and PFS advantage for a quadruplet treatment with daratumumab, bortezomib, melphalan and prednisone (Dara-VMP) [38]. In our cohort, 6% of MM patients aged ≥75 years treated at our center underwent an ASCT. In the CIBMTR analysis of 2092 patients aged ≥70 years, 28% of MM patients at this age group underwent an ASCT [27]. Our study does not prove ASCT is the optimal consolidation strategy for MM patients aged ≥75 years.

Limitation of our study is its retrospective nature and the small and highly selected cohort of patients, all relatively fit patients, suggesting that the low TRM and low admission rates should be interpreted with caution. Also, the study was not powered for subgroup analysis (such as melphalan dose). We have no reliable data about the number of days with fever. Another limitation is that none of the patients in our cohort was treated with quadruplets.

In conclusion, we demonstrate that ASCT is efficacious and can be safely delivered in the outpatient setting in carefully screened patients aged 75 or above. An arbitrary cutoff for age should not be used to exclude patients from ASCT, rather a careful assessment of "physiological age" including performance status and co-morbidities is required by an experienced treating team.

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Compliance with ethical standards

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References

1. Attal M, Richardson PG, Rajkumar SV, San-Miguel J, Beksac M, Spicka I, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019;394:2096–107.
2. Usmani SZ, Nahi H, Plesner T, Weiss BM, Bahlis NJ, Belch A, et al. Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: final results from the phase 2 GEN501 and SIRIUS trials. Lancet Haematol. 2020;7:e447–e55.
3. Mateos MV, Nahi H, Legiec W, Grosicki S, Vorobyev V, Spicka I, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol. 2020;7:e370–e80.
4. Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, Yee AJ, Huff CA, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. N. Engl J Med. 2019;381:727–38.
5. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95:548–67.
6. Kumar SK, Callander NS, Hillengass J, Liedtke M, Baljevic M, Campagnaro E, et al. NCCN guidelines insights: multiple myeloma, version 1.2020. J Natl Compr Cancer Netw. 2019;17:1154–65.
7. Koreth J, Cutler CS, Djulbegovic B, Behl R, Schlossman RL, Munshi NC, et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. Biol Blood Marrow Transplant. 2007;13:183–96.
8. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med. 1996;335:91–7.
9. Moreau P, Touzeau C, Vij R, Goldsmith SR, Rosko AE. Newly diagnosed myeloma in 2020. Am Soc Clin Oncol Educ Book. 2020;40:1–15.
10. Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015;125:2068–74.
11. Belotti A, Ribolla R, Cancelli V, Crippa C, Bianchetti N, Ferrari S, et al. Transplant eligibility in elderly multiple myeloma patients: prospective external validation of the international myeloma working group frailty score and comparison with clinical judgment and other comorbidity scores in unselected patients aged 65-75 years. Am J Hematol. 2020;95:759–65.
12. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv52–iv61.
13. Ghilardi G, Pabst T, Jeker B, Müller R, Cairoli A, Müller AMS, et al. Melphalan dose in myeloma patients ≥65 years of age undergoing high-dose therapy and autologous stem cell transplantation: a multicentric observational registry study. Bone Marrow Transplant 2019;54:1029–37.
14. Marini C, Maia T, Bergantim R, Pires J, Aguiar E, Guimarães JE, et al. Real-life data on safety and efficacy of autologous stem cell transplantation in elderly patients with multiple myeloma. Ann Hematol. 2019;98:369–79.
15. Mizuno S, Kawamura K, Hanamura I, Sunami K, Mori T, Nakamura F, et al. Efficacy and safety of autologous stem cell transplantation in patients aged ≥65 years with multiple myeloma in the era of novel agents. Bone Marrow Transplant. 2019;54:1595–604.
16. Merz M, Neben K, Raab MS, Sauer S, Egerer G, Hundemer M, et al. Autologous stem cell transplantation for elderly patients with newly diagnosed multiple myeloma in the era of novel agents. Ann Oncol. 2014;25:189–95.
17. Auner HW, Szydlo R, Hoek J, Goldschmidt H, Stoppa AM, Morgan GJ, et al. Trends in autologous hematopoietic cell transplantation for multiple myeloma in Europe: increased use and improved outcomes in elderly patients in recent years. Bone Marrow Transplant. 2015;50:209–15.
18. Cavo M, Gay F, Beksac M, Pantani L, Petrucci MT, Dimopoulos MA, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol. 2020;7:e456–e68.
19. Stadtmauer EA, Pasquini MC, Blackwell B, Hari P, Bashey A, Devine S, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 trial. J Clin Oncol. 2019;37:589–97.
20. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538–48.
21. Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016;127:2955–62.
22. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328–e46.
23. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M. SEER cancer statistics review, 1975–2016. https://seer.cancer.gov/csr/1975_2017/results_merged/topic_med_age.pdf.
24. Gertz MA, Ansell SM, Dingli D, Dispenzieri A, Buadi FK, Elliott MA, et al. Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative. Mayo Clin Proc. 2008;83:1131–8.
25. Wiebach H, Gezer D, Brummendorf TH, Crysandt M, Wilop S. Tolerability of high dose chemotherapy and autologous stem cell transplantation in elderly patients with multiple myeloma: a single-center retrospective analysis. Current Res Transl Med. 2020;68:139–44.
26. Dhakal B, Nelson A, Guru Murthy GS, Fraser R, Eastwood D, Hamadani M, et al. Autologous hematopoietic cell transplantation in patients with multiple myeloma: effect of age. Clin Lymphoma Myeloma Leukemia. 2017;17:165–72.
27. Munshi PN, Vesole D, Jurczyszyn A, Zaucha JM, St Martin A, Davila O, et al. Age no bar: A CIBMTR analysis of elderly patients undergoing autologous hematopoietic cell transplantation for multiple myeloma. Cancer. 2020;126:5077–87.
28. Yip HM, Yong K, De-Silva D, Rabin N. Assessing the safety of autologous stem cell transplant pathway via ambulatory care for patients with multiple myeloma. Hematol Oncol Stem Cell Therapy. 2020. https://doi.org/10.1016/j.hemonc.2020.01.001.

29. Shah N, Cornelison AM, Saliba R, Ahmed S, Nieto YL, Bashir Q, et al. Inpatient vs outpatient autologous hematopoietic stem cell transplantation for multiple myeloma. Eur J Haematol 2017;99:532–5.
30. Nath CE, Trotman J, Tiley C, Presgrave P, Joshua D, Kerridge I, et al. High melphalan exposure is associated with improved overall survival in myeloma patients receiving high dose melphalan and autologous transplantation. Br J Clin Pharmacol. 2016;82:149–59.
31. Sidiqi MH, Aljama MA, Buadi FK, Warsame RM, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation for light chain amyloidosis: decreased early mortality over time. J Clin Oncol. 2018;36:1323–9.
32. Gay F, Engelhardt M, Terpos E, Wäsch R, Giaccone L, Auner HW, et al. From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives. Haematologica. 2018;103:197–211.
33. Dold SM, Möller MD, Ihorst G, Langer C, Pönisch W, Mügge LO, et al. Validation of the revised myeloma comorbidity index and other comorbidity scores in a multicenter German study group multiple myeloma trial. Haematologica. 2020. https://doi.org/10.3324/haematol.2020.254235.
34. Cook G, Royle KL, Pawlyn C, Hockaday A, Shah V, Kaiser MF, et al. A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile): a development and validation study. Lancet Haematol. 2019;6:e154–e66.
35. Milani P, Vincent Rajkumar S, Merlini G, Kumar S, Gertz MA, Palladini G, et al. N-terminal fragment of the type-B natriuretic peptide (NT-proBNP) contributes to a simple new frailty score in patients with newly diagnosed multiple myeloma. Am J Hematol. 2016;91:1129–34.
36. Offidani M, Corvatta L, Polloni C, Centurioni R, Visani G, Brunori M, et al. Assessment of vulnerability measures and their effect on survival in a real-life population of multiple myeloma patients registered at Marche Region Multiple Myeloma Registry. Clin. Lymphoma Myeloma Leukemia 2012;12:423–32.
37. Murillo A, Cronin AM, Laubach JP, Hshieh TT, Tanasijevic AM, Richardson PG, et al. Performance of the International Myeloma Working Group myeloma frailty score among patients 75 and older. J Geriatr Oncol. 2019;10:486–9.
38. Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020;395:132–41.
39. Voorhees PM, Kaufman JL, Laubach JP, Sborov DW, Reeves B, Rodriguez C, et al. Daratumumab, lenalidomide, bortezomib, & dexamethasone for transplant-eligible newly diagnosed multiple myeloma: GRIFFIN. Blood. 2020;136:936–45.
40. Paquin AR, Kumar SK, Buadi FK, Gertz MA, Lacy MQ, Dispenzieri A, et al. Overall survival of transplant eligible patients with newly diagnosed multiple myeloma: comparative effectiveness analysis of modern induction regimens on outcome. Blood Cancer J. 2018;8:125.
41. Fiala MA, Foley NC, Zweegman S, Vij R, Wildes TM. The characteristics, treatment patterns, and outcomes of older adults aged 80 and over with multiple myeloma. J Geriatric Oncol. 2020;11:1274–8.
42. Bashir Q, Chamoun K, Milton DR, Khan M, Ahmed S, Mehta R, et al. Outcomes of autologous hematopoietic cell transplantation in myeloma patients aged ≥75 years. Leuk Lymphoma 2019; 60:3536–43.
43. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv. 2017;1:282–7.
44. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N. Engl J Med. 2019;380:2104–15.