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Research Article

Elderly (> 70 years) Multiple Myeloma Patients Benefit Equally from Autologous Hematopoietic Stem Cell Transplantation When Compared to Younger Patients

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Abstract

Autologous Hematopoietic Stem Cell Transplantation (AHSCT) performed after induction therapy is the standard of care for newly diagnosed Multiple Myeloma (MM) patients who qualify. Our institution has performed AHSCT for MM since 1991, and in this study, we sought to retrospectively examine the outcomes of 303 MM patients who underwent AHSCT from 1991-2021. We focused on Overall Survival (OS) and Progression-Free Survival (PFS) in patients in addition to Landmark survival (1-year post-transplantation). We found that in elderly patients > 70 years of age there was no significant difference in OS at 12 years, with 51% for patients < 70 years of age and 50% > 70; these were the same numbers for PFS at 12 years as well. We also found that median overall survival is improving overall with each decade in our transplanted MM patients with patient survival improved to over > 80% regardless of age at 7 years, when the previous median overall survival was 6 - 6.6 years before 2001. Given our findings, supported by others, we show that survival is continually improving over time in MM AHSCT patients and that AHSCT can be performed safely with equivalent landmark and long-term PFS and OS in patients of advanced age.

More Information

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Keywords: Multiple myeloma; Autologous stem cell transplantation; Long-term transplant survival; Advanced age patients

Introduction

Multiple Myeloma (MM) is a plasma cell malignancy that accounts for around 10% of all hematologic malignancies and is responsible for about 1% of all cancer deaths each year [1]. Diagnosis is made when there is a serum M-protein level of > 3 g/dL or >10% plasma cells in the bone marrow with associated end-organ damage. Treatment for MM has progressed significantly over the last 80+ years. Alkylating agents were first introduced as a treatment for MM in the 1940s [2,3] and have remained a mainstay as a component of treatment regimens with the addition of steroids in the 1960s [4]. It is worth noting that before the introduction of alkylating agents median survival of multiple myeloma patients was less than a year [5]. Further advancements include the implementation of Thalidomide/Lenalidomide and proteosome inhibitors which became crucial elements of treatment regimens in the late 1990's - early 2000's [6,7].

While these medication regimens successfully put many patients with MM into remission and improved mortality for a time, high-dose induction chemotherapy followed by Autologous Hematopoietic Stem Cell Marrow Transplant (AHSCT) is now the standard of care for eligible patients due to improved survival. The first successful syngeneic bone marrow transplant for MM was reported by Osserman, et al. in 1982 [8]. Later that decade Barlogie et al. treated refractory MM with a high dose of anthracycline with whole-body irradiation before autologous stem cell transplantation, and afterward developed a regimen with high-dose therapy followed by transplantation. This became the foundation for the now standard treatment for multiple myeloma when this was shown via randomized trials to prolong survival [9-11].

Multiple follow-up studies have examined MM patient's long-term response/survival after AHSCT with some even comparing outcomes over decades [12-18]. Others

have examined and demonstrated the safety and efficacy of AHSCT in MM patients of older age [19-24]. However, there often remains a bias in transplanting patients of advanced age, reflected in either the exclusion or lack of adequate representation of patients based on age with the introduction of new treatments (25,26). Additionally, there remains a dearth of data regarding long-term survival (> 10 years) of patients of advanced age (> 70 years) compared to their younger counterparts. Our institution first began bone marrow transplantation for MM patients in 1991, and in this retrospective analysis, we examine our findings of over 30 years of AHSCT for MM, with a focus on the long-term survival in a subset of patients over 70 years of age compared to those under 70 years.

Materials and methods

We retrospectively reviewed the records of 303 multiple myeloma with First Response (FR), partial response (PR), very good partial response (VgPR), or Complete Response (CR) who underwent AHSCT at Advocate Lutheran General Hospital between July 1, 1991, and December 31, 2021. The consent form signed by patients and approved by the Lutheran General Institutional Review Board allowed permission to share individual patient data with reporting agencies and potential publications. All patients met the criteria of being candidates for AHSCT, which required an ECOG performance status of greater than 2. The following laboratory values to be met hemoglobin of > 10.5 grams/dL, white blood cell count > 3000 cells per microliter, absolute neutrophil count of > 1500 cells per microliter (mcl), platelets g > 100,000 cells per mcl, Alanine Transaminase (ALT), aspartate aminotransferase (AST), bilirubin and alkaline phosphatase < 1.5 times normal limit. The following cardiac and pulmonary measurements are to be met left ventricular ejection fraction as determined by either an echocardiogram or gated heart scan of > 50%, normal pulmonary function tests where a minimum diffusing capacity of lungs for carbon dioxide (DLCO) of > 70%. Informed consent was obtained in all 303 patients as per institutional policy and in granting consent patients allowed the review of their records, report results to CIMBTR, and allow publications. Once patients consented to AHSCT, they underwent placement of either a Vascath TM catheter (Bard, Salt Lake City, Utah) or a Hickman Trifusion catheter (Beckton Dickson, Franklin Lakes, NJ). Following catheter placement, patients received Filgrastim 10 microgram/kg for 4 consecutive days starting on a Thursday. In 2008 plexifor was added to filgrastim.

Apheresis and CD 34 + collection

In the years from 1991 to 1994, apheresis commenced after 4 days of filgrastim to yield a mononuclear cell collection of 6x108 cells per kg. In 1994, apheresis commenced when the CD34 count by flow cytometry was equal to or greater than 20 cells per microliter. Apheresis was performed with the goal of a 6 L exchange initially on a COBE spectra system and since 2000 on Spectra Optia. A minimum of 2X106 CD+34 cells/kg were collected and cryopreserved.

Induction chemotherapy regimens

Preparative regimens utilized were vincristine, doxorubicin, and high-dose dexamethasone (VAD); lenalidomide, bortezomib, and dexamethasone (RVD); cyclophosphamide, bortezomib, and dexamethasone (CyBorD); and daratumumab plus lenalidomide, bortezomib, dexamethasone (Dara-VRD).

Conditioning regimen

The preparative regimen used was high dose Melphalan given on days -1 and -2. Melphalan was dosed based on creatinine clearance (Crcl). For patients with a Crcl of greater than 40ml/minute the Melphalan dose was 100mg/M2 on days -2 and -1 and for patients with a Crcl of less than 40 ml/minute, the dose was 70 mglm2 on days -2 and -1.

Supportive care

Following the administration of Melphalan and the reinfusion of peripherally harvested hematopoietic stem cells on day 0, patients were started on prophylactic ciprofloxacin 500mg two times daily starting on day +1 in conjunction with fluconazole 400mg daily until engraftment (ANC > 500 for 3 days). Filgrastim was started at a dose of 5 mg/kg on day +1 until 2012 when it was started on day +5 and continued until engraftment.

Follow-up and response to AHSCT

Patients were followed up closely following discharge and were seen weekly for the first month then every two weeks for another month and then monthly until day 100. Response to AHSCT was determined on day 100 by a repeat bone marrow exam and in 2010 a PET scan in addition to the bone marrow exam. The following day 100 patients were followed once every 3 months with a physical exam, complete blood count, comprehensive metabolic panel, serum protein electrophoresis, and since 2010 plasma cell profile. These visits were conducted every 3 months until year 10, and then once every 6 months. Progression-Free Survival (PFS) and overall survival (OS) were measured from day 0 until relapse of death of any cause. OS and PFS were calculated by Kaplan-Meier plots. PFS and survival between groups was conducted by log-rank analysis and differences were accessed by a generalized Wilcoxon test [27]. Landmark survival statistics were measured at 1-year post-transplantation.

Results

Between 1991 and 2021, 303 patients with multiple myeloma underwent AHSCT at Advocate Lutheran General Hospital. There were 158 males and 145 females with a median age of 67 years (range 30 years - 80 years). There

were 45 patients over 70 years of age (range 70 years - 84 years), of which 24 were male and 21 were female. Induction regimens utilization breakdown: VAD regimen *n* = 20, RVD regimen *n* = 205, CyBorD *n* = 41; and Dara-VRD *n* = 37 (Table 1). A complete response rate post-bone marrow transplant was found in 245 patients (81%) with 58 patients having no further response to treatment (Table 1). At 10 years, OS and PFS for all patients were both 31% (Figure 1, Table 2). The median PFS for patients less than 70 years was 4.7 years versus 4.6 years for patients 70 years and older (Figure 2, Table 2). The median OS for patients less than age 70 was 7.8 years *vs.* 54% at 10 years in patients over the age of 70 (Table 2). In patients that achieved landmark status: PFS at 12 years was 51% *vs.* 50%, and OS at 12 years was also 51% *vs.* 50% (Figures 3,4; Table 2).

Broken down by decade: 1991-2011 the median survival less than 70 years versus those over 70 years was 6.6 years *vs.* 6 years, respectively; in 2001-2011 the median survival was 8.45 years, versus those not yet reached 12 years for patients over 70 years; and 2011-2021 survival at 7 years was 91% *vs.* 80%, respectively (Table 3).

Serious adverse events grade 1 to 2 were reported for diarrhea, nausea, vomiting, and mucositis. Serious adverse events grade 3 included sepsis *n* = 7, with the sepsis breakdown of Staphylococcus epidermidis *n* = 2, Escherichia coli *n* = 4, multidrug-resistant Staphylococcus aureus *n* = 1,

Table 1: Baseline Characteristics, Initial Therapy before AHSCT, and Response.

Characteristic	All *n* = 303
Median Age, years (range)	67 (30 - 80)
Sex, n	
Male	158
Female	145
Induction Therapy at Diagnosis, n	
VAD	20
RVD	205
CyBorD	41
CartizRD/Dara-RVD:VD	37
Response Rate to Treatment, n (%)	
CR rate post-AHSCT	245 (81%)
No Arm Status	58 (19%)

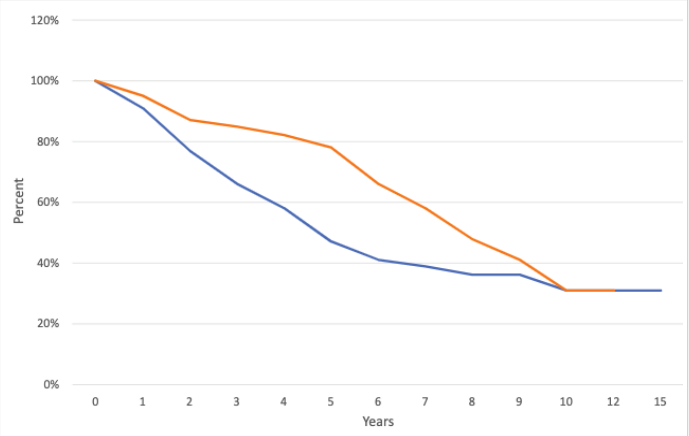

Figure 1: Progression-free Free Survival (blue line) and Overall Survival (orange) for all patients at 15 years.

Table 2: Comparative Survival Statistics of Patients over or under 70 years age.

	Under age 70 years (*n* = 303)	Over age 70 years (*n* = 45)
Median PFS, years	4.6	4.7
Median OS, years	7.8	54% at 10 years (Median survival NYR)
Survival + PFS at 10 years, %	31%	
Projected 15-year PFS, %	31%	
Landmark Survival at 1 year, n (% total)	156 (51%)	22 (49%)
PFS in LS subset, % survival at 12 years	51%	50%
OS in LS subset, % survival at 12 years	51%	50%

PFS = Progression Free Survival, OS = Overall Survival, NYR = Not Yet Reached, LS = Landmark Survival

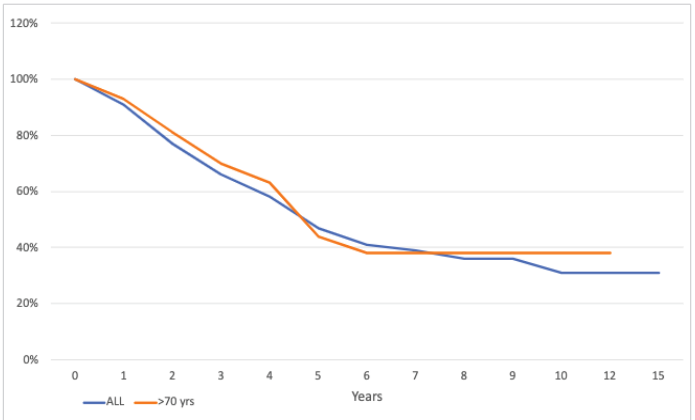

Figure 2: Progression Free Survival for patients < 70 years (blue line) vs. > 70 years (orange line).

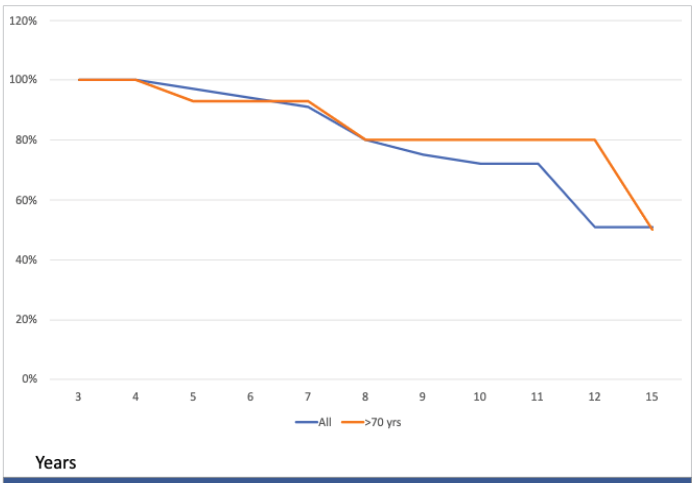

Figure 3: Landmark Overall Survival for patients < 70 years (blue line) vs. > 70 years (orange line).

Clostridium difficile *n* = 5. Other grade 3 serious adverse events included atrial fibrillation *n* = 4, acute kidney injury *n* = 2, deep vein thrombosis *n* = 1, and typhlitis *n* = 9. Long-term adverse outcomes include colon cancer at 6.5 years, prostate cancer at 3.8 years, renal cell carcinoma at 2.0 years, myelodysplastic syndrome at 11 and 13 years, breast cancer at 13 years, and lung cancer at 4 years. Toxic deaths occurred in 4 patients (1.3%). Etiologies of toxic deaths included typhlitis and E. coli with sepsis in 2 patients each (Table 4).

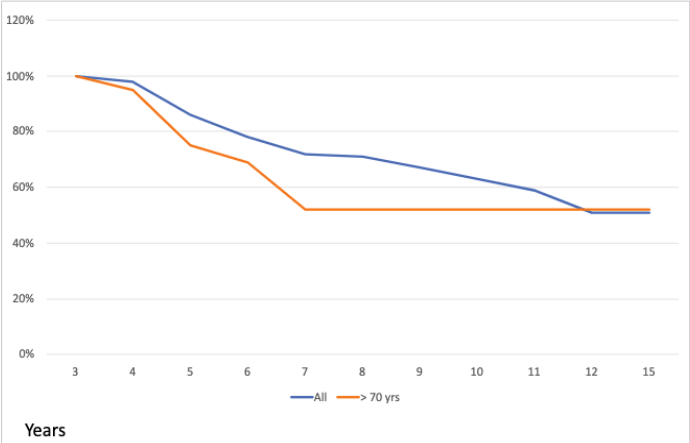

Figure 4: Landmark Progression Free Survival patients < 70 (blue line) vs. > 70 years (orange line).

Table 3: Median Survival by Decade at 12 Years with Age Comparison

	Under age 70 years	Over age 70 years
1991-2011, years	6.6 years	6 years
2001-2011, years	8.45 years	not yet reached 12 years
2011-2021, % at 7 years	91%	80%

Table 4: Adverse Events Following Transplantation.

Serious Adverse Events (SAE)	All (*n* = 303)
SAE Grade 1-2	
Diarrhea	
Nausea and Vomiting	
Mucositis	
SAE Grade 3, n	
Sepsis*	7
Clostridium Difficile	5
Atrial Fibrillation	4
Acute Kidney Injury	2
Deep Vein thrombosis	1
Typhlitis	9
Toxic Deaths, n	
Total	4
Typhlitis with sepsis	2
Escherichia Coli with sepsis	2
Long Term Malignancies	
Cancer Type, **Years After Transplant**	
Colon Cancer	6.5
Prostate Cancer	3.8
Renal Cell Carcinoma	2
Myelodysplastic Syndrome	11, 13
Breast Cancer	13
Lung Cancer	4

*Of sepsis patients: Staphylococcus Epidermidis *n* = 2, Escherichia Coli *n* = 4, Multidrug Resistant Staphylococcus Aureus *n* = 1.

Discussion

This retrospective study demonstrates our institutional effort to treat patients with multiple myeloma and details the following important findings: 1) Autologous stem cell transplant (AHSCT) can be performed effectively in patients with MM that qualify, with median and long-term survival improving as decades pass 2) Patients transplanted over 70 years of age have comparable progression-free survival and overall survival at 12 years compared to their younger counterparts.

Multiple Myeloma is a hematologic malignancy that affects many worldwide, and there has been a substantial progression in treatment over the last few decades. For patients who qualify, bone marrow transplantation after chemotherapy offers an increase in survival for their disease, and for many can provide a "functional cure" that allows them to live with this disease for years after diagnosis. This has led to an increased interest and examination of the length and depth of PFS and OS in these patients. Our study similarly showed an improvement in the median long-term (12-year) survival of transplanted patients with each decade. Many studies have also looked at survival outcomes and demonstrated similar conclusions. In 2008 Kumar, et al. performed a study that examined survival from diagnosis and after relapse in patients following AHSCT. When they compared median survival from 2000 - 2006 to the decade prior, they found that survival had improved by 50% (to almost 4 years). However, this improvement in survival was primarily in patients under 65, with survival for patients over 65 being inferior if they were to relapse [13]. Nishimura examined MM AHSCT patients from 1989 - 2018, and they found superior OS with reduced excess risk for MM-related death in patients treated in 2014 and later compared to patients treated in 1997 or earlier [14]. Many explanations for this phenomenon have been postulated. Many of the improvements in survival coincide with the implementation of newer induction therapies. Additionally, advancements in supportive care and newer treatments for chronic diseases and infections have been developed during this time and play a role.

While care of transplanted patients has improved tremendously over this time as detailed above, there are still many independent factors that determine whether an MM patient is appropriate for AHSCT. This includes performance status, blood counts, and cardiac and lung functionality. There is unfortunately also a pervasive thought that age should be a factor as well in this decision-making. Our study results however demonstrated the opposite of this notion. We found that progression-free survival, as well as landmark PFS and OS in patients that achieved landmark survival was equivalent in patients over 70 years of age compared to their younger counterparts (30 years - 69 years). This is especially important in this disease process where the median age of diagnosis of MM is approximately 69 years of age [28]. There have been multiple smaller retrospective studies that have compared survival in MM AHSCT patients with advanced age and most have consistently shown comparable disease response rates and overall survival at 5 and 10 years in patients of advanced age [21,22,29,30]. These studies have however shown mixed results regarding PFS, with some showing no significant difference between age groups and some showing inferiority in elderly patients. Larger scale

studies have also been done one examined over 11,000 myeloma AHSCT patients and compared survival outcomes at 1,2, and 3 years for patients > 70 years of age compared to 18 years - 59 years, and 60 years - 69 years and found that advanced age was not associated with worse non-relapse mortality (NRM), relapse rate, or PFS [20]. A particularly interesting study done by Munshi, et al. examined outcomes of patients > 70 years of age compared NRM, PFS, and OS compared to reference group < 65 years. At two years they found that NRM, relapse rate, and PFS were similar in the older group. However, they also found that post-relapse survival and OS were inferior [19]. What makes our study unique is the successful survival that we have demonstrated in the subset of patients that achieve landmark 1-year survival, more than 10 years post-transplant, one that we do not believe has been described in the literature in this way previously.

This study has limitations. It was conducted retrospectively at a single institution. It was conducted over 30 years, and pre-treatment regimens were not uniform across the entire subset, with the treatment of complications also evolving over this time. Admittedly, the sample size of patients over 70 years of age is smaller than those under 70. Additionally, NRM and rates of relapse were not examined in this study. It should also be noted that while many studies have findings consistent with our own, there have also been studies showing the contrary. One study showed inferiority in over 70 patients regarding post-relapse survival and OS, the former we did not measure, and the latter is contrary to our findings [20]. Another found a significantly worse 5-year survival in older *vs.* younger patients (65 years). However, this was only in the patients transplanted before 2014. There was no statistical difference in 5-year survival between these two groups in patients who began treatment after 2014 [14]. Another study found that older age at diagnosis was a significant risk factor for relapse-related mortality with a hazard ratio (HR) of 1.15 (p = 0.01) [13]. Future study directions include further examination of multiple myeloma in older patients over 70 years of age post-HSCT regarding patient characteristics and other complications outside of survival after transplantation compared to their younger cohorts. Like prior studies that have been performed, it would be worthwhile to further examine survival and patient characteristics impacting survival by decade to see if there has been a change regarding patients of advanced age.

There are almost continuous improvements in the care of myeloma patients (31) and elderly patients need not be excluded.

Conclusion

We present a retrospective single-institution experience with autologous hematopoietic stem cell transplantation for patients with multiple myeloma. In our patient set from 1991 - 2021, we observed that overall median survival improved over time. We also found that patients over 70 years of age who achieve landmark survival have equivalent survival statistics to their younger cohorts. This data indicates there has been improvement over time in maximizing survival in these patients during and after transplantation. Additionally, our data also supports that age alone does not impact long-term mortality in multiple myeloma patients who undergo AHSCT and should not be the primary factor in the decision-making of whether to transplant these patients.

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