Multiple Myeloma

Abstract 2195

Autologous Stem Cell Transplantation in Multiple Myeloma Patients Older Than 65 Year-Old, 12-Years Analysis of National Cancer Database

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Introduction. The diagnosis of multiple myeloma (MM) is often made in elderly individuals (median age at diagnosis 69 years) with over a third of patients exceeding 75 years of age. Many elderly patients are frequently excluded from clinical trials because of predefined upper age limit of 65 years limiting accessibility to autologous stem cell transplant (ASCT) for a large proportion of MM patients. Based on limited multicenter studies and randomized clinical trials in this population, we used the National Cancer Database (NCDB) to assess the outcomes of ASCT in MM patients older than 65 years of age.

Methods. We queried the NCDB for patients with MM diagnosed between 2004-2015 treated with ASCT as frontline therapy, yielding a final cohort of 9,383 patients. Multivariable logistic regression was used to determine the likelihood of receiving ASCT. Overall survival (OS) was calculated from the date of diagnosis to the date of last contact or death using Kaplan Meier methodology. Adjusted hazard ratios (HR) and 95% confidence interval (CI) are reported, with α=0.05 used to indicate statistical significance.

Results. The median age was 67.0 (range: 19-90). The majority of patients were older than 65 (58.5%), male (54.7%), Caucasian (75.6%), had government insurance (88%) and had a Charlson-Deyo Comorbidity score (CDCS) of 0 (75.5%). In addition to older age, insurance status, low annual income higher CDCS were associated with lower chances of receiving ASCT (Table 1). Patients in Urban areas (OR 1.377, CI 95% 1.286-1.475), and patients in Academic/Research Centers (OR 4.379 were CI 95%, 3.852-4.978) were more likely to receive ASCT. In patients younger than 65-years of age rate of ASCT was 7.0% in 2004 and increased to 16.7% in 2015. The annual rate of ASCT in patients older than 65-years of age was 1.1% in 2004 and increased to 4.7% in 2015. The multivariable cox proportional hazards of death in patients receiving ASCT was associated with improved survival (HR 0.492, CI 95% 0.473-0.512). Age (>65 years old HR 1.184, 95% CI 1.053-1.331), insurance status (uninsured HR 1.361, CI 95% 1.302-1.422, Medicaid HR 1.365, 95% CI 1.318-1.414, Medicare HR 1.271, 95% CI 1.244-1.299) and higher comorbidity score were associated with worse survival (Table 2). Median survival in patients younger than 65-years old receiving ASCT was 102.6 month versus 66.6 months in patients not receiving ASCT (HR 0.596, 95% CI 0.568-0.624) (Figure 1). Median survival in patients older than 65 years old and not receiving ASCT was 86.3 months versus 28.4 months in patients not receiving ASCT (HR 0.344, 95% CI 0.0320-0.371).

Conclusions. The findings of the present study demonstrate decreased utilization of ASCT in older patients with MM, despite significant survival benefit of such therapy. Other factors associated with decreased likelihood of ASCT are such as insurance status and annual income unfold existing disparities in patients with MM receiving ASCT.

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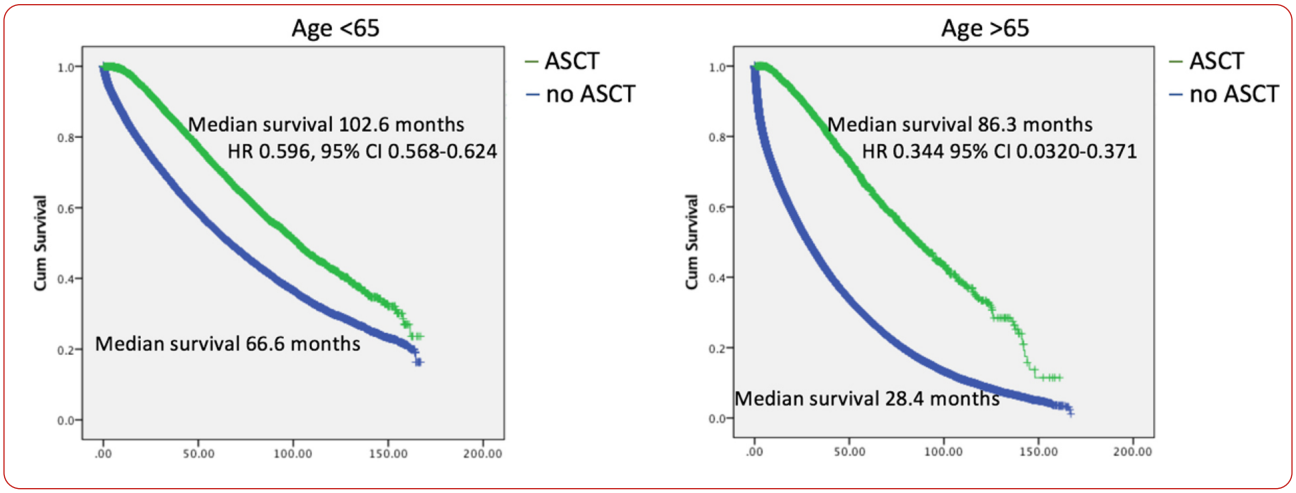

Figure 1. Survival analysis in MM patients in different age groups of ASCT recipients.

The Advanced Practitioner Perspective: Amy Pierre, ANP-BC

One established risk factor for the development of multiple myeloma is advanced age: the average age at diagnosis is 69 and one third of patients are over the age of 75. Given the fact that the majority of multiple myeloma patients are older, using the age cutoff of 65 for stem cell transplantation excludes the majority of patients who could potentially benefit from this therapy in the newly diagnosed setting. As time has passed, eligibility for stem cell transplant has shifted further from age and closer towards the concept of "fit vs. frail," with frail patients deemed ineligible.

By analyzing 12-year data on the usage of autologous stem cell transplants, this abstract uncovered that between the years of 2004 and 2015, the usage of autologous stem transplants has increased only by 3.5% in patients over the age of 65. This abstract also demonstrated that the median overall survival for patients over the age of 65 who received an autologous stem cell transplant was nearly 5 years longer than that of patients in the same age subset who did not receive a transplant. Risk factors that led to the decreased usage of stem cell transplant were older age, insurance status, lower income, and increased comorbidities. Those who were likely to receive a stem cell transplant were patients treated in an academic center or living in an urban setting.

Implications for the Advanced Practitioner

These data suggest that there is a subset of older patients who are eligible for stem cell transplants in the newly diagnosed setting who are not receiving this highly effective form of therapy. As an advanced practitioner, it is important to not rely solely on age as a cutoff factor when determining candidacy for a stem cell transplant for older patients, but rather their performance status and true ability to tolerate a stem cell transplant.

As for patients who are in a rural setting, underinsured, or considered lower income, advanced practitioners can assist in providing resources to help these at-risk patients obtain a stem cell transplant consult in an academic center so that they can have the opportunity to benefit from the survival advantage demonstrated by stem cell transplants.

Abstract LBA-6

Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (RRMM): Primary Analysis Results from the Randomized, Open-Label, Phase 3 Study Candor (NCT03158688)

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Introduction: The use of lenalidomide (LEN) and bortezomib (BTZ) in newly diagnosed multiple myeloma (MM) patients (pts), along with continuous or maintenance therapy paradigm have improved survival outcomes. However, many pts progress while on these agents or discontinue them due to toxicity. There is a need for novel, efficacious, and tolerable regimens that can treat MM pts who are exposed or refractory to LEN or BTZ. The proteasome inhibitor carfilzomib and the anti-CD38 monoclonal antibody daratumumab have both been approved as single agents or as components of combination regimens for the treatment of RRMM. The combination of carfilzomib, dexamethasone, and daratumumab has been shown to be efficacious and safe in RRMM in the phase 1 study MMY1001 (Chari, *Blood* 2019). We present results from the primary analysis of CANDOR, a multicenter, phase 3, randomized study comparing carfilzomib, dexamethasone, and daratumumab (KdD) vs carfilzomib and dexamethasone (Kd) in RRMM pts.

Methods: RRMM pts with measurable disease who had received 1-3 prior lines of therapy, with partial response or better to ≥1 line of therapy were eligible. Pts were randomized 2:1 to KdD or Kd. All pts received carfilzomib (K) as a 30-min intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m² on days 1 and 2 during cycle 1 and 56 mg/m² thereafter). Daratumumab (8 mg/kg) was administered IV on days 1 and 2 of cycle 1 and at 16 mg/kg once weekly for the remaining doses of the first 2 cycles, then every 2 wks for 4 cycles (cycles 3 to 6), and every 4 wks thereafter. All pts received 40 mg dexamethasone oral or IV weekly (20 mg for pts >75 years). The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall response rate (ORR), minimal residual disease (MRD) negative-complete response at 12 months (threshold, 10-5 cells), overall survival (OS), time to response, and safety.

Results: 466 pts (KdD: 312; Kd: 154) from 102 sites worldwide were randomized. Baseline characteristics were balanced between the two arms. Median age was 64 years. Of the randomized pts, 42.3% and 90.3% received previous LEN- and BTZ-containing regimens, respectively. 33% of pts were LEN-refractory. The primary endpoint of PFS was met after a median follow-up of 16.9 mo and 16.3 mo for the KdD and Kd arms, respectively. Median PFS was not reached for the KdD arm vs 15.8 mo for the Kd arm (HR, 0.63; 95% CI, 0.46-0.85; *P*=0.0014; Figure). PFS HRs favored KdD vs Kd across prespecified subgroups. Importantly, median PFS (KdD vs Kd) was not reached vs 12.1 mo in the LEN-exposed group (HR, 0.52; 95% CI, 0.34-0.80), and was not reached vs 11.1 mo in the LEN-refractory group (HR, 0.45; 95% CI, 0.28-0.74). Median time to first response was 1 mo in the KdD and Kd arms. ORR was 84.3% vs 74.7% (*P*=0.0040), and the rate of complete response or better was 28.5% vs 10.4%. MRD-negative complete response rate at 12 mo was 12.5% for KdD vs 1.3% for Kd (*P*<0.0001). Median OS was not reached in either arm at a median follow-up time of 17 mo (HR, 0.75; 95% CI, 0.49-1.13; P=0.08). Median treatment duration was longer in the KdD than Kd arm (70.1 vs 40.3 wks). The incidence of grade ≥3 AEs was 82.1% and 73.9% in the KdD and Kd arms, respectively. Serious AEs occurred in 56.2% (KdD) and 45.8% (Kd). The rate of treatment discontinuation due to AEs was similar in both arms (KdD, 22.4%; Kd, 24.8%). The frequency of grade ≥3 cardiac failure was 3.9% (KdD) and 8.5% (Kd); rate of cardiac failure event leading to K discontinuation was similar in the arms (3.9% and 4.6%). 5 deaths were reported as treatment-related, all in the KdD arm (pneumonia, sepsis, septic shock, acinetobacter infection, and cardio-respiratory arrest [n=1 each]). Additional efficacy endpoints, including key subgroup analyses will be presented.

Conclusion: KdD resulted in a significant PFS benefit over Kd, with a 37% reduction in the risk of

progression or death. Pts treated with KdD achieved deeper responses, with a nearly 10-times higher MRD negative-complete response rate vs Kd-treated pts. The PFS benefit of KdD was maintained across prespecified clinically important subgroups, particularly among LEN-exposed and LEN-refractory pts. AEs were generally manageable and the incidence of AEs leading to treatment discontinuation was similar in the arms. Overall, KdD was associated with a favorable benefit-risk profile and represents an efficacious new regimen for RRMM, including for LEN-exposed and/or LEN-refractory pts.

The Advanced Practitioner Perspective: Amy Pierre, ANP-BC

Immunomodulatory drugs (such as lenalidomide) and proteasome inhibitors (such as bortezomib) have become routinely used for the management of newly diagnosed multiple myeloma (MM). Lenalidomide maintenance has also become widely adopted to improve progression-free survival (PFS) and overall survival. The natural course of the disease lends to relapse, in which many patients become resistant to these therapies or have to discontinue therapy due to toxicity. Therefore, we need novel therapeutic combinations to successfully treat patients with relapsed/refractory MM who can no longer achieve benefit or are unable to tolerate lenalidomide or bortezomib.

CANDOR Study

A phase III study, CANDOR, analyzed PFS of relapsed/refractory MM patients being treated with the combination daratumumab, carfilzomib, and dexamethasone vs. a standard combination of carfilzomib and dexamethasone. Patients in this trial had to have received one to three prior lines of therapy and were randomized 2:1 to receive daratumumab with carfilzomib and dexamethasone vs. carfilzomib and dexamethasone alone.

This is a novel therapeutic approach combining an anti-CD38 monoclonal antibody, a second-generation proteasome inhibitor, and a steroid for patients who had previous exposure or intolerance to lenalidomide or bortezomib (one third of patients in the study were refractory to lenalidomide). Patients were given the opportunity to receive split dosing of daratumumab at 8 mg/kg for cycle 1 on days 1 and days 2 vs. the standard 16 mg/kg on cycle 1 day 1.

Study Results

The median PFS was not reached for the daratumumab combination, whereas it was 15.8 months for patients in the carfilzomib and dexamethasone arm. The PFS rates across all subgroups favored the triplet arm. The PFS endpoint for patients who were exposed to lenalidomide or refractory to lenalidomide in the carfilzomib and dexamethasone arm was about 1 year, whereas for the daratumumab-based arm it was not reached; this highlights that the addition of daratumumab to carfilzomib and dexamethasone can enhance PFS for this patient population.

Deep and durable responses were achieved, as patients in the daratumumab arm were twice as likely to achieve a complete response and nearly 10 times as likely to obtain minimal residual disease negativity at the 1-year time point.

Implications for the Advanced Practitioner

Advanced practitioners (APs) should consider this novel triplet option for patients who are relapsed/refractory and have had prior exposure, intolerance, or were refractory to lenalidomide, which is increasingly becoming an issue as patients are on lenalidomide maintenance therapy and are being treated with lenalidomide in the newly diagnosed setting.

It is important to note that this is an all-IV regimen, so patients who are candidates for this therapy must be able to regularly come to the cancer center for treatments twice weekly. In addition, this trial demonstrated that daratumumab can be given as a split dose efficaciously and safely, which is a nice option for treatment centers and for patients who may have difficulties accommodating a lengthy infusion.

The incidence of grade 3 or higher AEs was about 10% higher in the daratumumab-based arm, but the rates of discontinuation of treatment due to AEs were similar between both arms of therapy. The incidence of cardiac failure was less than 10% overall, but was interestingly higher in the carfilzomib and dexamethasone arm vs. the daratumumab-based arm. Mortality in this trial was primarily infection-related; therefore, the AP should advise patients regarding standard infection precautions and be cognizant of serious infectious that may occur.

Abstract 1893

Efficacy of Isatuximab with Pomalidomide and Dexamethasone in Elderly Patients with Relapsed/Refractory Multiple Myeloma: Icaria-MM Subgroup Analysis

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Introduction: Multiple myeloma (MM) is most frequently diagnosed among people aged 65-74, and approximately one-third of patients (pts) are aged ≥75 years. Advanced age has a negative effect on the prognosis of pts with MM. The randomized, open-label, active-controlled, multicenter phase 3 ICARIA-MM study (NCT02990338) compared treatment with the anti-CD38 monoclonal antibody isatuximab (Isa) in combination with pomalidomide and dexamethasone (Pd) with Pd. Pts had relapsed/refractory MM (RRMM) after ≥2 prior lines of therapy, including lenalidomide and a proteasome inhibitor. This subgroup analysis of ICARIA-MM examined efficacy and safety in elderly pts (≥75 years) compared with younger pts.

Methods: Pts were randomized (1:1) to receive Isa-Pd or Pd. Isa (10 mg/kg IV) was given on days 1, 8, 15, and 22 (cycle 1), and days 1 and 15 in subsequent 28-day cycles. All pts received pomalidomide 4 mg on days 1-21 of each cycle and dexamethasone 40 mg (20 mg for pts ≥75 years old) on days 1, 8, 15, and 22 of each cycle. The primary endpoint was progression-free survival (PFS), assessed by an independent response committee. Subgroup analyses were conducted for pts aged <65, 65-74, and ≥75 years of age.

Results: Overall, 307 pts were randomized to Isa-Pd (n=154) or Pd (n=153) and included in the intent-to-treat population. The median age of pts was 68.0 years in the Isa-Pd arm and 66.0 years in the Pd arm. In the Isa-Pd and Pd arms, there were 54 (35%) and 70 (46%) pts <65 years of age, 68 (44%) and 54 (35%) pts 65-74 years of age, and 32 (21%) and 29 (19%) pts ≥75 years of age, respectively.

In the overall population, PFS was significantly improved with Isa-Pd versus Pd (median 11.53 vs 6.47 months; hazard ratio [HR] 0.596; 95% confidence interval [CI] 0.436-0.814; p=0.001). Consistent with this, pts ≥75 years of age had a median PFS of 11.40 with Isa-Pd vs 4.47 months with Pd (HR 0.479; 95% CI 0.242-0.946). Similarly, in the Isa-Pd and Pd groups, pts 65-74 years of age had a PFS of 11.57 and 8.58 months (HR 0.638; 95% CI 0.385-1.059); in pts <65 years of age, PFS was 11.53 vs 5.03 months, respectively (HR 0.656; 95% CI 0.401-1.074).

Overall response rate (ORR) for all pts was 60.4% with Isa-Pd and 35.3% with Pd with an odds ratio (OR) of 2.80 (95% CI 1.72-4.56). ORR by age group in pts receiving Isa-Pd vs Pd was: 53.1% and 31.0% in the ≥75 years group (OR 2.52; 95% CI 0.79-8.26); 64.7% and 38.9% in the 65-74 years group (OR 2.88; 95% CI 1.29-6.46); and 59.3% and 34.3% in the <65 years group (OR 2.79; 95% CI 1.26-6.20).

At least a very good partial response (≥VGPR) was achieved by 31.8% of pts with Isa-Pd and 8.5% with Pd, with an OR of 5.03 (95% CI 2.51-10.59). Rates of ≥VGPR by age in pts receiving Isa-Pd vs Pd was: 31.3% and 0% in the ≥75 years group (OR not calculated); 32.4% vs 13.0% in the 65-74 group (OR 3.21; 95% CI 1.17-9.70); and 31.5% and 8.6% in the <65 years group (OR 4.90; 95% CI 1.64-16.35). Of 8 pts with negative minimal residual disease at 10−5, 2 were ≥75 years old.

At the time of analysis, overall survival (OS) data are not yet mature. However, in the elderly population, 8/32 (25%) pts in the Isa-Pd arm had died with median OS not reached, and in the Pd arm, 15/29 (51.7%) had died with a median OS of 10.25 months (HR 0.404; 95% CI 0.171-0.956).

In the Isa-Pd arm, the incidence of all-grade treatment-emergent adverse events (TEAEs) across age groups was: <65 years, 98.1%; 65-74 years, 100%; and ≥75 years, 100%. There were more Grade ≥3 TEAEs with Isa-Pd in pts aged ≥75 years (93.8%) compared with pts <65 years of age (85.2%), with a similar trend observed in the Pd arm (75.0% and 64.7%, respectively). There were also more treatment discontinuations because of TEAEs in pts ≥75 vs <65 years of age in the Isa-Pd arm (15.6% and 7.4%, respectively) and in the Pd arm (14.3% and 10.3%). There was a higher incidence of serious TEAEs (SAEs) in pts ≥75 vs <65 years of age in both arms (Isa-Pd, 68.8% and 57.4%; Pd, 57.1% and 47.1%, re-

spectively). The incidence of TEAEs with fatal outcome was lower in pts aged ≥75 years in the Isa-Pd arm (6.3%) than in pts <65 years (11.1%), while the opposite trend was observed with Pd (14.3% vs 5.9%).

Conclusion: The addition of Isa to Pd improved PFS, ORR, ≥VGPR, and OS in elderly pts, consistent with the benefit observed in the overall study population. There was a consistent trend toward higher rates of SAE and discontinuation due to TEAEs in elderly pts in both the Isa-Pd and Pd arms, but with no increase in fatal AEs in the Isa-Pd arm.

The Advanced Practitioner Perspective: Sandra E. Kurtin, PhD, ANP-C, AOCN®

The median age of newly diagnosed multiple myeloma (MM) patients is 68, so this represents a group of patients who tends to be older. In the relapsed/refractory setting, we have several options, including novel agents. This is an important phase III international randomized trial evaluating a second-generation anti-CD38 monoclonal antibody (isatuximab) in combination with the standard of care (pomalidomide and dexamethasone) to pomalidomide and dexamethasone alone.

In this study, 307 patients with a median age of 68—fitting that characteristic median age for MM—were randomized to receive either the three-drug regimen or the two-drug regimen. Importantly, more than 50% of these patients were over the age of 65. The primary endpoint for the study was progression-free survival. Progression-free survival in the three-drug regimen group was almost double that seen in the two-drug regimen group (11.5 months vs. 6.47 months, respectively). Interestingly, when considering patients over the age of 75, progression-free survival was 11.1 months for the three-drug regimen vs. 4.47 months in the two-drug regimen.

The secondary endpoint of overall response rate also favored the three-drug regimen, with 60.4% vs. 35.3% response. When considering depth of response (whether or not patients achieved a very good partial remission [VGPR] or greater), 31.8% of patients on isatuximab, pomalidomide, and dexamethasone had a VGPR or better compared with only 8.5% receiving the two-drug regimen of pomalidomide and dexamethasone.

Importantly, part of the inclusion criteria was previous treatment with lenalidomide and a proteasome inhibitor. This is a very important study for advanced practitioners, knowing that although patients have had prior treatment with novel agents, we have new options, and we now have our second anti-CD38 antibody for these patients.

Adverse Events

As with any clinical trial, there must always be a balance of safety and efficacy. In the subgroup analysis of patients aged ≥ 75, the rates of treatment-related adverse events were more common when compared with patients < 65 years of age in both treatment arms (Isa-Pd, 68.8% and 57.4%; Pd, 57.1% and 47.1%, respectively). Discontinuation rates due to adverse events were more common in patients ≥ 75 compared with < 65 years of age in the Isa-Pd arm (15.6% and 7.4%, respectively) and in the Pd arm (14.3% and 10.3%, respectively).

Including older patients in this clinical trial and then conducting the subgroup analysis is a very important first step toward understanding how best to adapt therapy to improve tolerance in this group. Assuming that all patients met the inclusion/exclusion criteria prior to enrollment in the study, the incidence and severity of adverse events, time to onset, and strategies used for management are critical to postmarketing integration of newer agents.

Clinical Trial Enrollment

Multiple relapses remain inevitable for the majority of patients with MM. Despite the expanded number of treatment options for relapsed/refractory MM over the past decade, gaps in treatment options remain. This is particularly true for older patients. Clinical trials offer the path toward developing new therapies but will require inclusion of a broader age range of patients to improve application in the postmarketing setting, similar to this trial. Enrolling patients in trials is the second barrier that needs to be addressed.

A 2019 systematic review by Unger and colleagues including 13 studies and 8,883 cancer patients identified several structural and clinical barriers to clinical trial enrollment. Collectively, these barriers resulted in 77% of patients who had access to a clinical trial not

participating in one. For more than half of the patients (55.6%), a trial was not available, and almost one fourth of patients (21.5%) were ineligible for trials available at their centers.

Among the barriers to clinical trial enrollment identified by clinicians was the time required to enroll patients in a trial and time constraints. Patient barriers to enrolling in a trial included not having the trial offered by clinicians, fear of side effects, costs, logistical barriers and trial requirements, and a feeling of loss of control. Importantly, patients who were offered a trial agreed to enrollment more than 50% of the time. Advanced practitioners play a pivotal role in the clinical trials process. Clinical trials should always be considered for any patient requiring treatment, as they represent treatment options that may not otherwise be available to the patient and contribute to the continued development of new therapies.

Reference

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