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Myeloma in Elderly Patients: When Less Is More and More Is More

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OVERVIEW

Multiple myeloma (MM) is a plasma cell malignancy that occurs among older adults and accounts for 15% of all hematologic malignancies in the United States. Thirty-five percent of patients are diagnosed at age 75 or older. Novel therapeutics and routine use of autologous stem cell transplantation (ASCT) have led to substantial improvements in patient survival, although improvements have been more impressive among patients younger than age 65. Finding the balance between under- and overtreating elderly patients is one of the biggest challenges specific to them as a subgroup of patients with MM. Decision making about which therapies and their dose intensity and duration should be influenced by a patient's functional status, personal preferences, disease characteristics, and ability to tolerate therapy. ASCT should be considered for all patients younger than age 80, assuming that they are not frail. The attainment of a stringent complete response and minimal residual disease negativity is associated with improved progression-free and overall survival. Again, consideration of quality of life for these patients is paramount. Although there is a growing list of tools to sort through these issues, a fully integrated approach has not yet been finely tuned, leaving additional work to be done for the treatment of elderly patients with MM.

MM is a plasma cell malignancy that occurs among older adults and accounts for 15% of all hematologic malignancies in the United States.[1] The median age of diagnosis is 69 years; in the next 15 years, MM incidence is expected to double.[2,3] Thirty-five percent of patients are diagnosed at age 75 or older, including 10% at age 85 older.[4] Novel therapeutics and routine use of ASCT have led to substantial improvements in patient survival. The median overall survival (OS) improved from approximately 2 years in the era of conventional agents[5] (e.g., melphalan and prednisone) to 5 years in the main large phase III randomized trials that incorporated novel agents.[6,7] There is a disparity in survival, however, between the young and old.[8,9] Recent data demonstrate that patients with MM who are younger than age 65 have improved 10-year relative survival rates (19.6% vs. 35%; $p < .001$), yet patients age 75 or older have not shared the same survival advantages (relative survival rate, 7.8% vs. 9.3%; $p = .3$).[10] MM-related deaths overall are highest among patients age 75 or older, and early mortality is most common among those age 70 or older.[8,10] Survival disparities for older

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adults with MM are multifactorial, and factors that play a role include treatment allocation differences, therapy toxicity, drug discontinuation, and physiologic reserve or patient fitness. Herein, we review these factors, the role of ASCT, and the goal of achieving minimal residual disease (MRD) to improve outcomes for older patients with MM.

RESPECTING FRAILTY OR AGE: HOW DO WE DECIDE TREATMENT INTENSITY?

Treatment intensity and clinical decision making for patients with MM relies on chronologic age, comorbidities, and performance status.[10–12] These factors oversimplify the complexity of caring for older adults and are ofen unable to identify the heterogeneity associated with aging. Treatment stratification for MM has been age based, in which clinical trials of transplant versus nontransplant strategies are conducted for those younger or older than age 65, respectively. ASCT is considered the standard of care; however, transplantation is less frequently performed for adults age 65–74 and rarely in those age 75 or older.[13] Balancing the toxicities of transplantation with survival advantages is challenging for the older adult. ASCT recipients report variable improvement in health-related quality of life (HRQoL)[14] and substantial shortand long-term morbidity,[15,16] and they can develop nonmalignant late effects that negatively affect overall health and functional status.[17] Older adults with MM are vulnerable to adverse events associated with multidrug combinations, which can lead to dose reductions or cessation of therapy and are associated with poorer outcomes.[18] Elderly age and frailty are not synonymous. Identifying factors that contribute to poor physiologic reserve and make patients vulnerable to treatment toxicity are under active investigation in MM. Frailty is a clinical syndrome, distinct from disability and comorbidities, in which cumulative factors of unintentional weight loss, self-report of exhaustion, weakness, slow walking speed, and/or low physical activity confer worse survival when present.[19] Some MM studies suggest frailty as patients older than age 75 or younger patients with abnormal organ function[20]; others have suggested treatment strategies with dose-level reductions based on risk factors of age 75 or older, help with activities of daily living (ADLs), and/or end organ dysfunction.[21] Understanding risk stratification and physiologic age is critical to reducing disparities when treating older adults with MM.

A geriatric assessment (GA) is a valuable tool to identify frailty and resolve occult health factors among older adults with MM. A GA is a global evaluation of the health of an older adult, defined as an interdisciplinary diagnostic process to identify age-related medical, psychosocial, and functional limitations that results in a coordinated treatment plan.[22] A GA is a multidimensional evaluation of functional status, fall history, social support, cognitive and psychological status, sensory loss, nutritional status, and comorbidities. A GA can predict chemotherapy toxicity and survival for patients with cancer[23–25]; however, data on GA outcomes specifically among patients with hematologic malignancies are limited. Emerging data suggest that use of a GA aids in clinical decision making for patients with cancer. Table 1 depicts a set of tools often used in a cancer-specific GA.[21,26–38]

Each of these evaluations aims to identify occult factors, unique to aging, that contribute to adverse events for patients with cancer. GA tools are comprehensive metrics to accurately

assess risk of morbidity and mortality among cancer populations, independent of performance status and age among patients with solid tumors.[40–42] GA tools are established to identify vulnerable patients at risk for drug discontinuation and grade 2 to 3 nonhematologic toxicity among cancer populations,[43] and both factors are associated with inferior outcomes in MM populations.

Given multiple treatment options for MM and concerns for frailty and tolerance among older adults, a GA is a valuable prognostic tool. The International Myeloma Working Group (IMWG) used a simplified GA tool based on age, comorbidities (Charlson comorbidity index), ADLs, and instrumental ADLs for newly diagnosed older adults enrolled into nontransplant frontline clinical trials.[21] The IMWG developed a frailty score that classified patients as fit (score = 0; 39%), intermediately fit (score = 1; 31%), and frail (score ≥ 2; 30%), based on data from 869 elderly individuals with newly diagnosed MM registered in three prospective trials. Scores were predictive of death, progression, treatment discontinuation, and nonhematologic toxicities. Three-year OS was 84% for fit patients, 76% for patients with intermediate fitness, and 57% for frail patients. The cumulative incidence of grade 3 or higher nonhematologic adverse events at 12 months was 22% for fit patients, 26% for patients with intermediate fitness, and 34% for frail patients. The IMWG frailty score profiles were independent of treatment, cytogenetics, or stage in the MM population. In addition, the IMWG frailty profiles were recently validated and confirmed in an older real-world MM population.[44] Personalizing therapy based on patient fitness or frailty may improve patient outcomes among older adults. Another example includes the Freiburg comorbidity index, a frailty assessment tool based on Karnofsky performance status, lung disease, and renal disease by using the estimated glomerular filtration rate.[45] The Freiburg comorbidity index is predictive of survival independent of MM stage, therapy, and age ($p < .0015$).[46] Efforts to streamline GA tools for clinical use and the multidisciplinary process to guide treatment decisions are ongoing.[47] Therapy intensity can also be guided by the effect of treatment on HRQoL for older adults.

HRQoL is of critical importance in the MM population and HRQoL instruments are used to capture physical and mental health from a patient's perspective. Older adults are risk averse when it comes to cancer treatment and do not choose quantity of life over quality.[48] Older patients with MM experience different HRQoL burdens than agematched controls, with more deficits in social, physical, role functions, fatigue, pain, and dyspnea.[49] Disease-focused endpoints such as response rates and progression-free survival (PFS) remain central to clinical trials; however, HRQoL can be complementary to such endpoints and the US Food and Drug Administration has increasingly recognized HRQoL as an important endpoint for approval of new cancer therapy.[50] Quality-of-life tools can be difficult to interpret and clinical significance is centered on the minimal importance difference, a nonuniversal standard that varies based on the clinical context and population of interest.[51] Older adults with MM report some of the worst HRQoL symptoms compared with other cancers.[52] In the FIRST study, patients had baseline HRQoL evaluated using MM-specific tools (QLQ-MY20) and global health tools (QLQ-C30 and EQ-5D).[53] Both lenalidomide/dexamethasone and melphalan/prednisone/thalidomide showed improvement in pain and fatigue; however, lenalidomide/dexamethasone reached the minimal importance difference for pain, whereas melphalan/prednisone/thalidomide did not. HRQoL decreased at

progression and continuous lenalidomide/dexamethasone treatment was associated with improved PFS. Similarly, among older adults treated with melphalan/prednisone/lenalidomide-R, melphalan/prednisone/lenalidomide, or melphalan/prednisone, patients treated with melphalan/prednisone/lenalidomide-R had better PFS and clinically meaningful improvements in HRQoL but no improvement in OS compared with those treated with melphalan/prednisone/lenalidomide. Declines in HRQoL have also been reported with onset of therapy, which can be attributable to treatment toxicity, as reported in both the VISTA[54] and UPFRONT[54] studies. These results demonstrate that disease response is imperative, not only for survival but also for maintaining quality of life. HRQoL instruments and data are invaluable assessments of patient well-being and are increasingly being used in MM clinical trial evaluations.[55]

Development of a peripheral blood test to mark physiologic frailty would be a powerful tool for the field of MM, allowing for vulnerable individuals to be rapidly identified and treatment intensity ascribed accordingly. Biomarkers can be defined in many ways in MM and are used to describe disease biology, staging, or treatment response.[56] Many candidate biomarkers are also being explored in cancer care to estimate physiologic reserve and risk for chemotherapy and/or transplant toxicity.[57,58] Recently, N-terminal natriuretic peptide type B in combination with Charlson comorbidity index scores and ADLs were explored as predictive of survival for patients with newly diagnosed MM.[59] Patients were scored 0–3 based on frailty metrics and reported median OS from diagnosis was not reached (stage I, score 0), 58 months (stage II, score 1), 28 months (stage III, score 2), and 18 months (stage IV, score 3; $p < .0001$). Use of N-terminal natriuretic peptide type B as a novel biomarker was independent of revised International Staging System (ISS) stage, age, and traditional Eastern Cooperative Oncology Group (ECOG) performance status.[59] Other aging biomarkers of interest include measuring $p16^{INK4A}$ (p16), one of the most robust and validated aging biomarkers for patients with cancer.[60] *p16* inhibits cell cycle progression when cells are exposed to internal and external stressors[61–65] and prolonged expression leads to irreversible cell cycle arrest, termed cellular senescence. *p16* accumulates with age in a variety of human tissue types and increases more than 16-fold in peripheral blood T cells over the human lifespan.[66,67] Cytotoxic chemotherapy of MM ASCT is as sociated with molecular aging of peripheral blood T cells and the relationship with frailty is being explored.[58,68] The need for objective biomarkers of physiologic age is especially important in the MM population due to the age of affected individuals, heterogeneity of fitness in older adults, and diverse treatment strategies available.

In summary, chronologic age is not a limiting factor for deermining treatment of MM. Assessing patient fitness can be reconciled with use of a GA, a tool to identify frailty or vulnerabilities of treatment toxicity. However, comprehensive GA tools are underutilized in MM clinical trial design and in routine care, impeding personalized care for the older adult. HRQoL matters for older adults and clinicians must provide accurate interpretations of the patient experience with the data available to them. GA tools, in combination with novel peripheral blood aging biomarkers, are compelling and may standardize our approach to recognize the nuances of aging in the MM population.

ASCT FOR OLDER PATIENTS WITH MM: WHO IS NOT ASCT ELIGIBLE?

MM is the most common indication for ASCT in North America today. Although randomized trials have shown the benefit of high-dose melphalan for patients younger than age 65, this procedure is now routinely performed for patients up to age 80,[69,70] owing to recent advances in supportive care and the use of filgrastim-mobilized peripheral blood. However, fewer than 20% of all patients age 65 or older are undergoing the procedure.[13]

Rationale for Exploring ASCT for Older Patients With MM

In 2015, at age 65, the average man would be expected to live 17.9 more years on average, compared with 18 more years for a woman; at age 70, a man would be expected to live 14.1 more years on average, compared with 16.3 more years for a woman.[5] The depth of response is shown to increase survival both in the frontline and salvage settings and among both transplant-eligible and transplant-ineligible patients; this is particularly true for complete remissions and is now being shown for attainment of an MRD state.[71–76] Thus, pursuing high-dose melphalan with ASCT as a strategy that will allow for a deeper response for older patients is appropriate as long as the expected morbidity and mortality of the transplant process is acceptable. The major challenge is to identify a priori which older patients have the highest likelihood of developing severe complications and thus will not benefit from the procedure

Outcomes of Hematopoietic ASCT for Older Patients

ASCT is being performed more frequently for patients older than age 60, with improvements in NRM and overall outcomes. Table 2 summarizes the largest registry series published to date. These reports, together with multiple single-center reports, demonstrate that autologous ASCT is feasible for older patients with MM, that NRM is routinely less than 5%, and that results are comparable or only slightly inferior to those of younger patients.[77,78]

The number of autografts for older patients with MM has also increased dramatically in the last 10 years. Using data from the European Bone Marrow Transplant Registry, Auner et al[77] reported that from 1991 to 1996, a total of 381 patients with MM underwent autografting in Europe versus 6,518 in the 5-year period from 2006 through 2010. Even more dramatic is the increased activity among patients older than age 70, of which only two were reported to the European Bone Marrow Transplant Registry from 1991 to 1996, in contrast with 2,617 from 2006 to 2010. Of note, many of the patients older than age 65 received 200 mg/m^2 of melphalan without worse outcomes than younger patients.[77,78]

Complications of High-Dose Melphalan and Autologous ASCT for Older Patients

Table 3 summarizes the most common complications seen after administration of high-dose melphalan and the potential effects on older patients. Of note, atrial arrhythmias and supraventricular tachycardias are more common with high-dose melphalan than other conditioning regimens, and retrospective analysis has shown that increasing age is a predictor of this complication.[79]

Mucositis and gastrointestinal toxicities are the most common nonhematologic toxicities seen after high-dose melphalan and are not increased among the older population but relate directly to melphalan exposure. Nath et al[80] measured the melphalan area under the curve for 114 patients as part of a multivariate analysis; only a higher melphalan area under the curve predicted a higher rate of grade 3 and 4 mucositis, but it was also associated with improved survival. Although many centers reduce the dose of melphalan to 140 mg/m^2 for patients older than age 70, there are currently no data to suggest that this improves outcomes in this patient population.

How to Identify the ASCT-Ineligible Patient

In general, the criteria for ASCT candidates have been well defined.[81,82] However, which characteristics identify patients who should not be considered for this procedure have not been as well documented. In principle, older patients who should not be considered for high-dose melphalan and autologous ASCT consolidation would fall into one of four categories, as described below.

Patients in the first category may have performance status or comorbidities that may make it highly unlikely that they could benefit from high-dose melphalan consolidation. In 1992, Reuben et al[83] reported on the value of functional status in predicting mortality by conducting a 4-year prospective longitudinal follow-up study of functionally impaired community-dwelling elderly persons. A total of 282 elderly patients (age 64 or older) were included. Using scales from the functional status questionnaire, patients were assessed at baseline and at an average of 51 months later. In the multivariate model, the following baseline characteristics were independently predictive of death: greater dysfunction on a scale of intermediate ADLs, male sex, living alone, white race, better quality of social interactions, and age. Of note, patients unable to perform one of the ADLs had a 2-year mortality rate of 27%.

Based on the IMWG frailty criteria, a frail patient has a 34% chance of developing severe toxicity to regular induction chemotherapy[21]; this type of patient is unlikely to benefit from high-dose melphalan and should not be considered for that treatment modality.

The hematopoietic cell transplantation comorbidity index (HCT-CI) was developed by Dr. Mohamed Sorror to predict survival and NRM in the allogeneic setting. However, this index is also shown to also predict NRM risk after autografts. Saad et al[84] studied 1,156 autograft recipients after they received high-dose melphalan, using data reported to the Center for International Blood and Marrow Transplant Research. Participants were stratified into three risk groups: HCT-CI of 0 (42%) versus HCT-CI of 1–2 (32%) versus HCT-CI of more than 2 (26%). One-year NRM was low at 2% and did not correlate with HCT-CI score. On multivariate analysis, OS was inferior in groups with an HCT-CI of 1–2 or more than 2.[21] For younger patients, the Karnofsky performance status predicts for higher NRM and worse HCT outcomes.[21] Thus, our current recommendation is not to pursue high-dose melphalan for older patients with poor performance status (Karnofsky performance status of 80 or less).

Patients in the second category have such a good risk disease category that high-dose melphalan consolidation is unlikely to positively impact long-term outcomes, thus making

short-term side effects and negative impact on quality of life unacceptable. Patients with revised ISS stage 1 have an expected 5-year survival of more than 60%; thus, a 79-year-old patient with standard risk cytogenetics and revised ISS stage 1 who achieves a complete remission to induction therapy will not likely benefit from high-dose melphalan. Conversely, a 79-year-old patient with high-risk cytogenetics who has not achieved a PR to induction would benefit from this procedure.[85]

Patients in the third category have substantial socioeconomic or cultural barriers to safely undergoing high-dose melphalan treatment. Successful ASCT requires social and family support.[86] Thus, a thorough socioeconomic assessment should be done prior to proceeding to high-dose melphalan for older patients (particularly caregiver availability and whether the patient is the caregiver of an elderly spouse).

Patients in the final category do not desire to proceed to high-dose melphalan consolidation. Many older patients simply do not want to go through the time and effort required to undergo an ASCT. Obviously, this decision must be respected but should be preceded by a frank discussion of the risks and benefits of the procedure for each individual patient.

Future Directions for ASCT for Elderly Patients

High-dose melphalan and ASCT remain the standard of care for transplant-eligible patients around the world. However, the definition of transplant eligibility has changed. ASCT was initially limited to younger patients with normal or almost normal organ function, but it is now routinely performed for individuals up to age 80 (even those with substantial comorbidities, including end-stage renal disease).

However, high-dose melphalan with autologous ASCT is still associated with notable morbidity and a mortality rate that can be as high as 10% at 1 year for older and debilitated patients with a poor performance status. Considering that many alternative therapies exist for MM today, deciding whether to proceed to ASCT must be done carefully for an older patient in close collaboration with the patient, family members, and other health care professionals. Pretransplant GA has been shown to be helpful in deciding which patients have the highest likelihood of severe complications, but it is not definitive.

Aging biomarkers that can provide a reproducible measure of physiologic fitness are currently being explored. Such biomarkers include molecular markers, inflammatory markers, immunosenescence panels, serum and hematologic parameters, and hormones. Only large prospective trials will allow us to determine whether a specific biomarker panel will be sensitive enough to determine who will tolerate high-dose melphalan well and who will not. Likewise, for the older population that proceeds to ASCT, all efforts must be made to prevent untoward toxicity. These strategies, such as pharmacokinetically directed melphalan, preASCT rehabilitation and exercise training, as well as specific agents to ameliorate gastrointestinal and other toxicities, must be assessed prospectively.

In summary, high-dose melphalan can be successfully used for older patients with MM to increase their quantity and quality of life; however, its use should be determined by carefully assessing the risk/benefit ratio for each individual patient.

AIMING FOR A COMPLETE RESPONSE IRRESPECTIVE OF AGE

With a change in the treatment landscape for elderly patients, the goals for them have also been modified, with prolongation of disease-free survival and OS as important goals. The depth of response has emerged as a surrogate marker that is highly correlated with PFS and OS, and a large metaanalysis including 14 studies and 1,273 patients provided quantitative evidence to support the integration of MRD assessment as an endpoint in clinical trials of MM.[87] However, some patients that reach suboptimal response after therapy are relapse free at 10 years, raising an important question about whether a complete response (CR) is actually needed to achieve long-term survival. Indeed, biologically well-defined patient subgroups with monoclonal gammopathy of undetermined significance–like baseline profiles or specific molecular subtypes can present long-term survival without achieving a CR.[88] However, these patients represent only 10% of patients with MM. Thus, for the majority of patients, higher CR rates are needed to increase survival rates and responses of high quality are becoming optimal short-term endpoints that might potentially contribute to accelerating the approval of new agents.

The role of the conventional CR was evaluated in a retrospective analysis including 1,175 patients with newly diagnosed MM, enrolled in three multicenter trials, who were treated with melphalan/prednisone (332 patients), melphalan/prednisone/thalidomide (332 patients), bortezomib/melphalan/prednisone (VMP; 257 patients), or bortezomib/melphalan/prednisone/thalidomide (254 patients). After a median follow-up of 29 months, 3-year PFS and OS were 67% and 27% (hazard ratio [HR], 0.16; $p < .001$), and 91% and 70% (HR, 0.15; $p < .001$) for patients who obtained CR and in those who achieved very good partial response, respectively. Similar results were observed for patients older than age 75, and multivariate analysis confirmed that the achievement of a CR was an independent predictor of longer PFS and OS, regardless of age, ISS stage, and treatment.[89] In spite of these results, approximately 40% of the patients who achieved CR will relapse and 20% will die within 4 years after initial therapy; these data reflect that the definition of conventional CR (e.g., negative immunofixation in serum and urine, disappearance of any soft tissue plasmacytomas, and less than 5% plasma cells in bone marrow) failed to detect such differences. As a result, the stringent CR was added in 2006, based on the normalization of serum free light chains and absence of clonal plasma cells in bone marrow biopsies by immunohistochemistry and/or immunofluorescence; in 2016, new CR criteria have been defined, introducing the MRD evaluation by flow cytometry, next-generation sequencing (NGS), and imaging.[90] The question now is whether MRD evaluation is ready for prime time for elderly patients with MM.

Molecular assessments include the use of allele-specific oligonucleotide quantitative polymerase chain reaction or NGS of VDJ sequences. Puig et al[91] demonstrated that among newly diagnosed patients treated according to the PETHEMA/GEM2005MAS65 protocol (including VMP or VTP as induction followed by VT or VP as maintenance), those with a molecular CR after induction had a PFS not yet reached, whereas patients with MRD positivity had a significantly shorter PFS (median 31 months; $p = .03$). MRD levels were measured by allele-specific oligonucleotide polymerase chain reaction, and there was a good correlation with NGS-based approaches, Martinez-Lopez et al[92] established the prognostic

significance of achieving MRD negativity by deep sequencing for the same series of patients. In this study, among the patients with a CR, the MRD-negative group had a significantly longer time to progression compared with the MRD-positive group (median 131 vs. 35 months; p = .0009). Although a good correlation was reported between both molecular techniques, more than one-half of patients in clinical practice will not be evaluated by allele-specific oligonucleotide quantitative polymerase chain reaction because of the inability to detect a clone, unsuccessful sequencing, or suboptimal performance; however, the NGS approach will be applicable to more than 90% of patients and is thus the optimal molecular technique to be used considering 10^{-5} as the target cutoff level for the definition of MRD negativity.

Using multiparametric flow cytometry, only a few patients (15%) in the Medical Research Consortium Myeloma IX protocol for elderly patients achieved flow MRD negativity after induction regimens without proteasome inhibitors, and these individuals showed nonsignificantly superior PFS.[93] However, results of the Medical Research Consortium Myeloma XI protocol were recently reported and the flow MRD-negative rate was 14%, with no differences between cyclophosphamide, thalidomide, and dexamethasone and CRD. Patients achieving MRD-negative status had a significantly longer PFS but no differences were reported in terms of OS.[94] In contrast, in the PETHEMA/GEM2005MAS65 study, patients were monitored after six induction cycles; within a subset of 102 patients with a CR/very good partial response, 30% attained flow MRD negativity with PFS and OS rates at 3 years of 90% and 94%, respectively. These results were recently updated after a median follow-up of more than 5 years and show median PFS and OS rates not yet reached for patients with flow MRD negativity status after induction with VMP, but not after VTP.[95] Because patients with flow MRD negativity after two different regimens should experience similar outcomes, this study also revealed that the four-color multiparametric flow cytometry assay originally performed in these studies was underpowered for ultrasensitive detection of MRD. In recent years, the sensitivity has increased because of the simultaneous assessment of eight or more markers and evaluation of a greater number of cells, resulting in one of the most relevant prognostic factors, including among elderly patients with MM. Next-generation multiparametric flow cytometry was used to monitor MRD for 162 patients enrolled in the PETHEMA/GEM2010MAS65 study and treated with VMP and lenalidomide/dexamethasone during 18 months in a sequential (nine plus nine cycles) or alternating way (VMP, lenalidomide/dexamethasone, VMP, and so on). MRD status was an independent prognostic factor for time to progression (HR, 2.7; p = .007) and OS (HR, 3.1; p = .04), with a significant benefit for patients with flow MRD negativity (median time to progression not reached, 70% OS at 3 years), and similar poorer outcomes for patients with MRD levels, also considering the optimal cutoff level between 10^{-4} and 10^{-5}. Of note, flow MRD-negative status significantly improved time to progression for patients older than age 75, as well as for those with high-risk cytogenetics.[96] Table 4 provides a summary of the most relevant studies establishing a relation between CR or MRD negativity and outcome.

The aim of achieving CR in the bone marrow after treatment has an additional challenge because it is possible to have a patchy bone marrow infiltration or extramedullary involvement with flow or NGS MRD negativity in single bone marrow aspirates. New criteria adopted that ^{18}F-fluorodeoxyglucose PET-CT is a powerful tool to assess tumor

metabolic activity and the effect of therapy on tumor-cell metabolism.[90] Multiple studies support the notion that the detection of PET-positive lesions has prognostic value for patients with MM at diagnosis. However, all studies have been conducted thus far among young patients before and after transplantation and will be prospectively evaluated in the new trials with elderly patients.

In summary, MRD clearance into and also likely outside the bone marrow is achievable for elderly patients with MM in the era of novel agents because it is predictive of superior outcomes, and this concept has been shown to also apply to patients older than age 75. Achievement of MRD negativity for patients with high-risk cytogenetic abnormalities is relevant because their outcome is similar to that of standard risk.

TYING IT ALL TOGETHER FOR ELDERLY PATIENTS WITH MM

Decision making for the elderly patient with MM is not simple. Although attainment of MRD negativity is possible for a subset of elderly patients with MM, the group of elderly patients elderly is very heterogeneous and treatment remains challenging because of specific clinical and biologic features not withstanding frailty, comorbidities, and financial and psychosocial factors.[98] Is striving for CR or MRD negativity appropriate for all elderly patients with MM? Which regimens are best for this population?

Options for treatment of elderly patients abound. Current favorites, depending on region and drug availability, include lenalidomide/dexamethasone,[7] VRd,[99] VMP,[6] and ASCT. Triplet therapy including a proteasome inhibitor and an immunemodulating drug and ASCT is associated with the deepest responses and, in most instances, with better PFS and OS. Careful analyses of the combination of carfilzomib plus an immune-modulating drug have not yet been performed for elderly or frail patients. Although prolongation of disease-free and OS has historically been the ultimate goal, achieving prolonged treatment-free intervals, absence of treatmentrelated toxicity, and good quality of life have also become important aims for elderly patients. Recent developments in MM have focused on identifying these vulnerable patients through GA, including frailty, disability, and comorbidities.[21]

We are approaching an era in which we should be able to provide individualized treatment strategies and drug doses to improve tolerability and optimize efficacy and ultimately survival. Some studies have shown the value of MRD for evaluation of the efficacy and potential treatment decisions. Emerging work on immune profiling[96] in addition to MRD assessment may be a means to identify patients with poor, intermediate, and favorable outcomes and to guide us in decision making regarding the optimal type and duration of treatment for individual patients. All of these approaches are extremely relevant in the treatment of elderly patients with MM, and a frailty-adapted therapy together with a sensitive response assessment, including immune profiling, could help to deliver the appropriate regimen with the optimal duration avoiding underor overtreatment. This will require a cooperative effort toward new clinical trial designs in which patients are accurately stratified and assessed according to all of these important parameters.

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KEY POINTS

- Overall survival for elderly patients with MM is gradually improving, but at a slower rate than for younger patients.
- Assessment of frailty and geriatric assessments should play a role in treatment decisions.
- ASCT is a viable treatment option for nonfrail patients.
- Targeting minimal residual disease may be appropriate for the elderly patient population with MM, but the optimal balance between longevity and quality of life has not yet been established.
- Further clinical trials will be required to optimize decision making for this complex patient population.

TABLE 1.

Clinical Examples of Geriatric Assessment Metrics

Domain	Metric Example	Clinical Conclusion
Function	SPPB[26]	Impaired SPPB is associated with a twofold higher risk of death compared with those with a normal physical performance among populations with leukemia[27]
	TUG	Poor mobility by TUG predicts early mortality among cancer populations
	Handgrip strength[28]	Grip strength is an accurate and consistent predictor of all causes of mortality in middle-aged and elderly persons (RR, 0.89)[29]
	Brief Fatigue Inventory[30]	Fatigue strongly correlates with depression and is highly variable post-transplant[39]
	ADL/IADL	Deficits in ADL, combined with age and comorbidities among patients with MM, resulted in notable survival differences in patients[21]
Psychiatric	HADS[31]	Psychiatric morbidity results in a significantly longer length of hospital stay and influences recovery post-transplant[32]
Social	MOS Social Support Survey[31]	Social isolation and loneliness predict disease outcome and results in substantial impairment in psychologic and physical well-being[33]
		Social support structure impacts clinical outcomes and quality of life post-transplant.[34,35]
	3MS	Cognitive impairment demonstrates the greatest likelihood for mortality among older adults with leukemia[27]
		Attention deficits persist for up to a year following myeloma transplant[36]
Nutrition	MNA	Impaired nutritional status independently predicts early death in patients with newly diagnosed cancer at age 65 or older (OR, 2.77).
Comorbidities	Comorbidity calculator[38]	HCT-CI predicts nonrelapse mortality and survival in MM[37,38]

Abbreviations: SPPB, Short Physical Performance Battery; TUG, Timed Up and Go Test; ADL, activities of daily living; IADL, instrumental activities of daily living; HADS, Hospital Anxiety and Depression Scale; MOS, Medical Outcomes Study; 3MS, Modified Mini Mental State; MNA, Mini-Nutritional Assessment; RR, relative risk; MM, multiple myeloma; OR, odds ratio; HCT-CI, hematopoietic cell transplantation comorbidity index.

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TABLE 2.

Large Registry Studies of Outcomes of ASCT for Older Patients With Myeloma

Study	Year	Age (Years)	No. of Patients	Conditioning	NRM	OS at 2 Years
Auner et al[77]	1991–1996	60–64	383	Melphalan	3.9	62.5
		65–69	75		8.0	55.3
		> 70	2		NA	NA
	1996–2000	60–64	1,835		3.6	77.6
		65–70	718		4.1	71.9
		> 70	100		4.0	70.8
	2001–2005	60–64	4,253		2.4	81.1
		65–69	2,478		2.7	79.3
		> 70	497		2.4	72.7
	2006–2010	60–64	6,518		1.8	86.3
		65–69	3,860		2.1	82.9
		> 70	740		2.0	80.2
Sharma et al[78]	2008–2011	60–64	2,617	Melphalan	2.0	85
		65–69	2,049			83
		> 70	946			

Abbreviations: ASCT, autologous stem cell transplantation; NRM, non-relapse mortality; NA, not available; OS, overall survival.

TABLE 3.

Complications of High-Dose Melphalan

Complication	Incidence	Implications for the Older Patient
Myelosuppression	Universal, with the exception of truly nonablative regimens	Prolonged myelosuppression increases risks of life-threatening infections; thus, strategies that may accelerate neutrophil recovery in older patients could be beneficial.
		Filgrastim is beneficial in shortening the duration of neutropenia.
Mucositis	10%–20% with high-dose melphalan	Severe mucositis may require opioid analgesia for pain control, which is less well tolerated by older patients, Risk of aspiration from severe mucositis may be more frequent for older patients.
		Cryotherapy (ice chips) has been shown to reduce the risk of severe mucositis, Palifermin has not.
Infections	> 50% of patients will have some infectious complication, The most common is neutropenic fever or Gram-positive sepsis,	For older patients, the ability to recover from infectious complications may be affected by prior comorbid states and ability to tolerate anti-infective therapies such as foscarnet or amphotericin B.
		Older patients require the same infectious prophylaxis as younger patients; zoster prophylaxis is required until immunity is documented and may be required for life.
Gastrointestinal toxicities	Loss of appetite is almost universal	Gastrointestinal toxicities can be more common and more severe for older patients.
	Severe nausea and emesis are rare with current antiemetic regimens	It is essential to maintain good hydration and adequate electrolyte replacement.
	Severe diarrhea can be seen with melphalan	Nutritional intervention may need to be considered earlier.
Pulmonary toxicities	Pneumonitis and diffuse alveolar hemorrhage rare after high-dose melphalan	Patients with pre-ASCT pulmonary comorbidities are at higher risk for pulmonary toxicities.
Hepatic toxicities	SOS/VOD rare with high-dose melphalan	Similar risk as younger patients
Cardiac toxicities	Arrhythmias	Atrial fibrillation is a common occurrence after high-dose melphalan.
	Congestive heart failure	
Engraftment syndrome	Rash, fever, and occasionally diarrhea and renal dysfunction	Early institution of steroid therapy is important to prevent DAH.
Graft failure	Rare	Older patients collect a lower cell dose.

Abbreviations: SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease; ASCT, autologous stem cell transplantation; DAH, diffuse alveolar hemorrhage.

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TABLE 4.

Summary of the Most Relevant Studies Establishing a Relation Between CR or MRD Negativity and Outcomes

Method	LOD	No. of Patients	CR Rate	MRD− Status (%)	PFS (MRD− vs. MRD+)	p Value	OS (MRD− vs. MRD+)	p Value	Reference
Classic CR		1,175	17	—	67% vs. 27% (at 3 years)*	< .001	91% vs. 70% (at 3 years)*	< .001	Gay et al[89]
ASO-qPCR	10^{-5}	103		46	NR vs. 31 months	.002	NR vs. 60 months	.008	Puig et al[91]
NGS	10^{-5}	133**		27	80 months vs. 31 months	< .001	NR vs. 81 months	.019	Martínez-López et al[92]
6-color MFC	10^{-4}	245		15	10.5 months vs. 7.4 months	.1	NA	NA	Rawstron et al[93]
6-color MFC	10^{-4}	297		14	34 months vs. 18 months	< .0001	54 months vs. 50 months	.12	de Tute et al[94]
4-color MFC	10^{-4}	102		43	90% vs. 35% (at 3 years)	< .001	94% vs. 70% (at 3 years)	.08	Paiva et al[97]
8-color MFC	10^{-5}	162		34	NR vs. 15 months	.007	70% vs. 60% (at 3 years)	.04	Paiva et al[96]

*For the classic CR method, the PFS comparison was done between CR and very good partial response.

**This study included also patients who were transplant candidates but the results were similar for both groups of patients.

Abbreviations: CR, complete response; MRD, minimal residual disease; ASO-qPCR, allele-specific oligonucleotide quantitative polymerase chain reaction; NGS, next-generation sequencing; MFC, multiparametric flow cytometry; LOD, limit of sensitivity; PFS, progression-free survival; NR, not reached; OS, overall survival; NA, not available.

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