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Management of multiple myeloma in older adults: Gaining ground with geriatric assessment

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ABSTRACT

Multiple myeloma increases in incidence with age. With the aging of the population, the number of cases of multiple myeloma diagnosed in older adults each year will nearly double in the next 20 years. The novel therapeutic agents have significantly improved survival in older adults, but their outcomes remain poorer than in younger patients. Older adults may be more vulnerable to toxicity of therapy, resulting in decreased dose intensity and contributing to poorer outcomes. Data are beginning to emerge to aid in identifying which individuals are at greater risk for toxicity of therapy; comorbidities, functional limitations, and age over 80 years are among the factors associated with greater risk. Geriatric assessment holds promise in the care of older adults with multiple myeloma, both to allow modification of treatment to prevent toxicity, and to identify vulnerabilities that may require intervention. Emerging treatments with low toxicity and attention to individualizing therapy based on geriatric assessment may aid in further improving outcomes in older adults with multiple myeloma.

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1. Introduction

The incidence of multiple myeloma is increasing; with the aging of the population, there is projected to be a 90% increase in the

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Table 1a – Laboratory evaluation of suspected multiple myeloma.

Complete blood count
Comprehensive metabolic profile
Serum protein electrophoresis with immunofixation
Quantitative immunoglobulin levels (IgG, IgA, IgM)
Beta-2-microglobulin
Lactate dehydrogenase
Serum-free light chain assay
24-h urine collection for urine protein electrophoresis, urine immunofixation
Consider assessment of 25 hydroxy vitamin D levels

number of cases of multiple myeloma diagnosed annually in older adults by 2034.[1] Advances in treatment, particularly the introduction of novel therapeutic agents, have significantly improved overall survival in older adults with multiple myeloma over the past 2 decades.[2] However, improved efficacy of therapeutic approaches must be balanced with the risk of toxicity of therapy. Older adults may be particularly vulnerable to toxicity of therapy; grade III/IV toxicities of therapy are associated with poorer survival among older adults on clinical trials.[3] Adapting therapy to minimize toxicity may allow similar dose intensity and outcomes with lower toxicity, compared to more dose-dense strategies.[4] However, older adults remain at greater risk for early mortality and experience poorer survival than their younger counterparts,[2,5] highlighting the need for further research to optimize therapy in older adults with multiple myeloma.

2. Initial evaluation

The initial, disease-focused evaluation of multiple myeloma for older adults with suspected multiple myeloma is the same as in younger individuals.[6] This includes a history and physical examination, laboratory evaluation (Table 1a), imaging, bone marrow biopsy, and aspirate with conventional cytogenetics and fluorescence *in situ* hybridization for recurring chromosomal translocations and deletions/duplications seen in multiple myeloma. In addition to the "CRAB" diagnostic criteria of hypercalcemia, renal insufficiency, anemia, and bone lesions, recently updated indications for treatment of multiple myeloma now include ≥60% plasma cells on bone marrow biopsy or aspirate, a ratio of involved to uninvolved serum-free light chains ≥ 100 and more than 1 focal lesions on MRI (Table 1b).[7]

Establishing a diagnosis of multiple myeloma is not always straightforward in older adults. Comorbidities and intercurrent illnesses may confound the evaluation. Anemia may be attributable to a number of other causes, such as nutritional deficiencies, acute blood loss, and anemia of inflammation due to other medical conditions or even myelodysplasia, rather than evidence of end-organ damage caused by a malignant clonal proliferation of plasma cells. Attribution of anemia to multiple myeloma may require examination of historical laboratory values and exclusion of other etiologies, such as iron deficiency. Similarly, renal insufficiency may be related to comorbidities, such as hypertension or diabetes, rather than multiple myeloma; examining historical laboratory values for temporal trends in renal function and excluding recent exposure to nephrotoxins may aid in establishing whether renal insufficiency is related to a new diagnosis of multiple myeloma.

Following establishment of the diagnosis of multiple myeloma requiring therapy, staging should be determined. The International Staging System was developed as a simple prognostic tool, based on serum albumin and beta-2-microglobulin.[8] Subsequently, some authors have called into question its utility in stratifying prognosis in older adults with multiple myeloma.[9] More recently, the Revised International Staging System has been developed, which also incorporates serum lactate dehydrogenase levels and high-risk cytogenetic abnormalities (Table 2).[10] Of the more than 4000 patients included, one-third was over the age of 65. On multivariate analysis, the R-ISS remained prognostic, independent of age, suggesting that the R-ISS will have utility across the age spectrum in risk-stratifying patients.

Finally, the initial disease-focused evaluation should include assessment of chromosomal abnormalities. Genetic risk stratification helps direct treatment decisions and retains prognostic significance in the older patient. Shorter progression-free survival (PFS) and overall survival (OS) are seen with t(4;14) and del17p in both older and younger patients, although the incidence of t(4;14) decreases with age.[11] More investigation is needed to evaluate potential differences in myeloma genetics with aging.

Table 1b – Revised IMWG diagnostic criteria for multiple myeloma.

Definition of multiple myeloma
Clonal bone marrow plasma cells ≥10% or biopsy-proven plasmacytoma
Plus ≥1 myeloma-defining event(s):

- Any end-organ damage due to the plasma cell disorder(C)alcium—serum calcium >1 mg/dL upper limit normal or >11 mg/dL (>2.75 mmol/L)
  (R)enal—creatinine clearance <40 mL/min or serum creatinine >2 mg/dL <177 μmol/L
  (A)nemia—hemoglobin <2 g/dL lower limit normal or <10 mg/dL
  (B)one lesions—one or more osteolytic lesions on bone radiograph, CT, or PET/CT
- Any biomarker of malignancy (≥80% probability of end-organ damage within 2 years)Clonal bone marrow plasma cells ≥60%
  Involved (minimum ≥10 mg/dL) to uninvolved serum-free light chain ratio ≥ 100
  >1 focal lesion (≥5 mm in size) on MRI

Definition of smoldering multiple myeloma
Both criteria must be met

- Serum monoclonal protein (IgG or IgA) ≥3 g/L or urine monoclonal protein ≥500 mg/24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma-defining events or amyloidosis

Adapted from Rajkumar et al. Lancet Oncol 2014

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