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Management Of Frail Patients with Multiple Myeloma in the Era of Monoclonal Antibodies and Bispecific T-Cell Engagers (Bites)

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Introduction

As we navigate the therapeutic landscape of 2026, managing multiple myeloma (MM) in frail patients remains one of the most delicate challenges in hematologic oncology. Historically, a substantial proportion of these patients were deemed too frail for active treatment or were offered 'ultra-light' regimens that often lacked sufficient efficacy. However, the advent of monoclonal antibody-based regimens and T-cell redirecting re-evaluation of our clinical goals. In octogenarian and frail populations, we must strike a precise balance between achieving deep, durable responses and preserving quality of life. The paradigm has shifted from 'less is more' to 'precision-driven more,' where the objective is to deploy highly effective therapies in a dose-sculpted manner to maximize the therapeutic window, seamlessly integrating direct anti-neoplastic treatment with robust supportive care."

The Frailty Paradox: From Chronology to Biology

Historically, frailty in multiple myeloma (MM) was often synonymous with advanced chronological age.

However, our understanding has matured significantly, and the definition of frailty has evolved beyond

age-based metrics to dynamic biological assessments [1,2]. The modern geriatric assessment now integrates wearable-device-led performance tracking and digital health monitoring, allowing for a more granular understanding of a patient's "fitness" in real-time. We are no longer merely asking if a patient is transplant-ineligible; we are asking if their frailty is "fixed", stemming from irreversible cardiovascular or pulmonary comorbidities, or "reversible," driven by the myeloma burden itself, such as hypercalcemia, renal failure, or debilitating bone pain. This distinction is critical because "fitifying" a patient through rapid disease control, has become a primary therapeutic objective. The integration of "Minimal Residual Disease (MRD) monitoring" via Mass Spectrometry (MS) can revolutionize the management of the frail patient by providing a more nuanced longitudinal assessment of treatment response. MS-based "liquid biopsies" can detect monoclonal proteins (M-protein) at levels approximately 100 times more sensitive than traditional immunofixation (IFE). This high-resolution sensitivity may allow clinicians to distinguish between patients who require continuous therapy and those who may safely undergo de-escalation to mitigate cumulative toxicities and preserve physiological reserve [3]. For the frail individual, for whom repeated bone marrow aspirations often represent a significant procedural burden and physical stressor, the transition to MS-based blood monitoring offers a highly sensitive, minimally invasive alternative that aligns with the goals of patient- centered care and toxicity sparing.

Frontline Standards: The Era of "Frailty-Adapted" Quadruplets

The most pivotal evolution in the frontline treatment of transplant-ineligible (TI) patients is the emergence of quadruplet regimens. These combinations integrate immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and low-dose steroids with monoclonal antibodies (MoAbs).For years, the doublet of

lenalidomide and dexamethasone (Rd), or triplets containing IMiDs and proteosome inhibitors (e.g: lenalidomide, ixazomib and dexamethasone [4] or lenalidomide-bortezomib- dexamethasone (VRd-lite) served as the gold standard. However, more recent data reinforce that anti-CD38 MoAbs combined with IMiDs or modified PIs provide superior progression-free survival (PFS) without a prohibitive increase in

toxicity, provided that proactive dose-sculpting is employed [5 6].

Subsequent real-world analyses, including elderly patients [7] suggested that even in octogenarian population, the addition of a fourth agent can lead to unprecedented rates of high quality, long-term responses. The key to success in the frail population, however, is not the blanket application of these drugs but the "start low, go slow" or "stop early" strategies: [8] The Steroids Story: Dexamethasone remains the most "toxic" component for the frail, contributing to sleep disturbances, proximal myopathy, and increased infection risk. By using MRD-monitored response-adapted treatment, as pioneered in the MASTER trial, we may significantly reduce the "steroid burden" once a deep response is achieved [9]. Furthermore, the omission of steroids in frail populations has proven highly beneficial; by minimizing steroid-related toxicities, it facilitates greater treatment persistence with the primary anti-myeloma backbone therapy [10].

The Subcutaneous Revolution

The universal transition to subcutaneous formulations for bortezomib and anti-CD38 antibodies has been a gamechanger for the frail. This shift has not only improved patient convenience and clinical throughput but has also drastically reduced the incidence of infusion-related reactions and peripheral neuropathy, critical factors for maintaining independence and reducing the risk of falls in elderly patients.

Innovative Immunotherapy: Bispecifics and the "Frail-First" Approach

Perhaps the most transformative development is the use of bispecific T-cell engagers (BiTEs), such as Teclistamab, Elranatamab and Talquetamab , in the relapsed/refractory setting. Historically, we feared that the "cytokine storm" (CRS) associated with T-cell redirection would be catastrophic for frail patients. However, real-world data suggests that these therapies are not only feasible but highly effective even in the frail and very elderly patients. The MajesTEC-1 trial and subsequent follow-up studies have shown that with standardized step-up dosing and the prophylactic use of tocilizumab [11] , the rates of high-grade CRS in patients over 75 are comparable to younger cohorts. The overall response rates (ORR) in elderly populations have reached upwards of 70–80%, a staggering improvement over traditional "salvage" chemotherapy or older triplets [12-15]. Unlike CAR-T cell therapy which requires bridging therapy and apheresis, often taxing for the frail, bispecifics offer an "off-the-shelf" solution. This allows patients to remain in their communities, reducing the psychological and physical burden of travel to tertiary academic centers.

The Digital and Molecular Horizon: Reducing the Burden of Care

Looking forward, the "Holy Grail" for the treatment of frail MM patients lies in the reduction of " no- essential treatment, and non -essential tests, required for making clinical decisions ". The transition toward blood-based MRD monitoring, via Mass Spectrometry, is a cornerstone of this effort. This technology reduces the need for frequent, painful bone marrow biopsies, which can be a major stressor for an 80-year-old patient with osteoporosis. Furthermore, the integration of Artificial Intelligence (AI) in clinical decision-making is beginning to yield "Predictive Frailty Scores." These models analyze electronic health record data to predict which patients are likely to experience "treatment-induced frailty" versus those who will "fit-ify" under therapy. This allows us to transition from a conservative, palliative mindset to a more curative intent once the initial disease-driven frailty is reversed through rapid cytoreduction.

Integrating Palliative Care in the Modern Management of Multiple Myeloma

The integration of palliative and supportive care into the modern management of MM has evolved into a fundamental cornerstone of therapy, particularly for frail and octogenarian populations. Rather than being viewed as an alternative to anti-neoplastic treatment, early palliative involvement is now

recognized as a vital, concurrent component of care that addresses the multifaceted needs of vulnerable patients.

In octogenarians, the symptom burden of MM, including debilitating bone pain, fatigue, and renal

impairment, is frequently compounded by geriatric syndromes such as polypharmacy, cognitive decline, and physical frailty. For these patients, the primary clinical objective often shifts from achieving the

deepest possible molecular response to the achievement of good response along with the preservation of functional independence and quality of life (QoL) [16].

Integrating palliative care early in the disease course allows for a holistic approach that manages both disease-related symptoms and the cumulative toxicities of modern "dose-sculpted" regimens. Key elements of this supportive framework include [17]:

- Symptom Management and QoL: Early intervention for pain and fatigue is associated with improved treatment persistence and psychological well-being.

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- Bone Health and Infection Prophylaxis: Given the high risk of fractures and the immunocompromised state of octogenarians, aggressive supportive care (e.g., bisphosphonates and prophylactic anti-infectives) is essential to prevent secondary complications that often trigger a "frailty cascade."

- Advanced Care Planning: Facilitating early discussions regarding treatment goals ensures that therapeutic intensity aligns with the patient's values, particularly as they navigate the complexities of relapsed/refractory disease.

Conclusion

The management of the frail myeloma patient in 2026 is no longer an exercise in palliation, but a sophisticated exercise in precision medicine that integrates the anti-neoplastic therapy and supportive care. We have entered an era where we can achieve deep responses in octogenarians, provided we remain vigilant about the unique toxicities of our novel agents. By combining potent quadruplets and bispecific antibodies with rigorous, data-driven supportive care-including mandatory thromboprophylaxis, antiviral screening, and steroid-sparing regimens-we are finally closing the survival gap between the fit and the frail.As we continue to refine these strategies, the focus must remain on the patient's voice. Our quest for "zero-MRD" must always be balanced against the patient's ability to live a meaningful, independent, and dignified life.

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