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Risk-Adapted Systemic Treatment Strategies in Multiple Myeloma: A Narrative Review

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Abstract

Multiple myeloma is a biologically heterogeneous plasma cell malignancy characterized by highly variable clinical presentation, disease course and treatment response. Over the past two decades, the introduction of high-dose chemotherapy with autologous stem cell transplantation and the development of novel agents—including immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies—have substantially improved survival outcomes. Nevertheless, treatment selection remains challenging due to differences in patient fitness, comorbidities, frailty and disease-related risk factors.

This narrative review summarizes current evidence on risk-adapted systemic treatment strategies in multiple myeloma, focusing on therapeutic decision-making in newly diagnosed and relapsed/refractory disease. A comprehensive literature search was conducted using major biomedical databases to identify clinically relevant studies, guidelines and meta-analyses published between 2000 and 2024. Emphasis was placed on treatment approaches tailored to transplant eligibility, biological risk profile and patient-related factors.

Recent data support the use of combination regimens incorporating proteasome inhibitors, immunomodulatory agents and anti-CD38 monoclonal antibodies as standard therapy across different disease stages. High-dose chemotherapy followed by autologous stem cell transplantation remains the standard of care for eligible patients, while less intensive regimens are recommended for elderly or frail individuals. In relapsed or refractory disease, triplet or quadruplet regimens have demonstrated improved response rates and survival, although cumulative toxicity and treatment resistance remain major concerns.

In conclusion, modern management of multiple myeloma requires a personalized, risk-adapted approach that balances treatment efficacy with tolerability and quality of life. Ongoing advances in targeted therapies and risk stratification are expected to further refine treatment algorithms and improve long-term outcomes.

Keywords: multiple myeloma, medical treatment, high-dose chemotherapy, proteasome inhibitors, immunomodulators, monoclonal antibodies, transplantation.

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INTRODUCTION

Multiple myeloma is a malignant plasma cell disorder characterized by marked biological heterogeneity, variable clinical presentation and an unpredictable disease course. Despite major advances in diagnosis and treatment, the disease remains incurable in most patients and continues to represent a significant clinical challenge, particularly in elderly and frail populations. Bone involvement, anemia, renal dysfunction and immunodeficiency remain the most common disease-related complications and are major contributors to morbidity and reduced quality of life[2,15].

Over the past two decades, the therapeutic landscape of multiple myeloma has evolved substantially. The introduction of high-dose chemotherapy followed by autologous stem cell transplantation, together with the development of novel agents - including immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies - has led to deeper responses, prolonged progression-free survival and improved overall survival[19,23,30]. As a result, multiple myeloma has increasingly been transformed into a chronic disease characterized by sequential relapses and remissions rather than a rapidly fatal malignancy.

Nevertheless, optimal treatment selection remains complex. Therapeutic decisions must account for patient-related factors such as age, comorbidities, frailty and functional status, as well as disease-related characteristics including tumor burden, cytogenetic risk profile and treatment responsiveness. The increasing availability of effective combination regimens has further intensified the need for individualized, risk-adapted treatment strategies that balance efficacy with tolerability and long-term quality of life[22,23].

In this context, the present narrative review aims to synthesize current evidence on risk-adapted systemic treatment strategies in multiple myeloma. Emphasis is placed on contemporary approaches to treatment selection in newly diagnosed and relapsed or refractory disease, with particular attention to transplant eligibility, biological risk stratification and patient fitness.

MATERIALS AND METHODS

This narrative review was conducted to provide a clinically oriented synthesis of current evidence on risk-adapted systemic treatment strategies in multiple myeloma, in accordance with contemporary clinical practice and international guidelines. The methodological approach was designed to support qualitative evidence integration rather than a formal systematic review or quantitative meta-analysis.

A comprehensive literature search was performed using major biomedical databases, including PubMed/MEDLINE, SpringerLink, Scopus and the National Center for Biotechnology Information, supplemented by access to full-text publications through the HINARI program. The search strategy focused on articles published in English between 2000 and 2024 that addressed the diagnosis, systemic treatment and clinical management of multiple myeloma[2,6,19,22].

Search terms included "multiple myeloma" in combination with "systemic treatment," "risk-adapted therapy," "proteasome inhibitors," "immunomodulatory drugs," "monoclonal antibodies," and "autologous stem cell transplantation." These terms were selected to capture publications reflecting the evolution of modern treatment strategies and risk-based therapeutic decision-making[7,10,15,23].

Eligible publications comprised original clinical studies, randomized controlled trials, meta-analyses, narrative reviews and international clinical practice guidelines relevant to contemporary myeloma management. Study selection was guided by clinical relevance, methodological quality and contribution to current treatment concepts rather than by predefined quantitative inclusion or exclusion criteria. Particular emphasis was placed on large clinical trials, high-quality meta-analyses and consensus-based guidelines issued by international expert groups[11,22,30].

Reference lists of selected articles were manually reviewed to identify additional relevant publications not retrieved through the initial database search. Publications that did not align with the scope of the review, were outdated, or lacked relevance to risk-adapted systemic treatment strategies were excluded.

As this review was narrative in nature, no formal risk-of-bias assessment or quantitative data synthesis was performed. The findings were synthesized qualitatively, with emphasis on treatment strategies tailored to transplant eligibility, disease-related risk factors and patient fitness, reflecting real-world clinical decision-making in multiple myeloma[4,20,23].

RESULTS

Risk stratification and general treatment principles. The reviewed literature consistently emphasizes

the biological and clinical heterogeneity of multiple myeloma, which underpins the need for risk-adapted treatment strategies. Disease-related factors, including tumor burden, cytogenetic abnormalities and staging systems, as well as patient-related characteristics such as age, comorbidities, frailty and functional status, were identified as key determinants of treatment selection across all disease stages[7,22,23]. Contemporary guidelines and large clinical studies uniformly support individualized therapeutic decision-making rather than a uniform treatment approach[22,30].

Treatment strategies are generally structured into induction, consolidation and maintenance phases, with systemic therapy representing the cornerstone of disease management. The choice of regimen is primarily guided by transplant eligibility and overall risk profile[6,20].

Newly diagnosed multiple myeloma. Transplant-eligible patients.

For patients considered eligible for autologous stem cell transplantation, induction therapy based on combinations of proteasome inhibitors, immunomodulatory agents and corticosteroids represents the current standard of care. Multiple randomized trials and meta-analyses have demonstrated superior response rates, progression-free survival and overall survival with these regimens compared with conventional chemotherapy[10,19,23].

High-dose melphalan followed by autologous stem cell transplantation remains a widely accepted consolidation strategy in eligible patients. Evidence from comparative studies indicates improved survival outcomes with transplantation, particularly in younger patients and those with high-risk disease features[7,10]. Induction regimens incorporating anti-CD38 monoclonal antibodies have further improved depth of response, including rates of minimal residual disease negativity[11,22].

Maintenance therapy following transplantation, most commonly based on immunomodulatory agents, has been associated with prolonged disease control and delayed progression[15,23].

Transplant-ineligible patients. In transplant-ineligible patients, less intensive but effective systemic regimens are recommended. The literature supports the use of combinations based on lenalidomide or bortezomib, often in association with corticosteroids and, more recently, anti-CD38 monoclonal antibodies[6,11,22].

Randomized trials and network meta-analyses have demonstrated improved progression-free survival and overall survival with daratumumab-based regimens compared with traditional melphalan- and prednisone-based therapies [11,22]. Treatment duration, dose adjustments and regimen selection are tailored according to tolerability and patient fitness, with the goal of maintaining disease control while minimizing toxicity[4,20].

Relapsed and refractory multiple myeloma. Relapse is a defining feature of multiple myeloma and the reviewed studies highlight increasing disease aggressiveness and treatment resistance with successive relapses. No single standard regimen has been established for relapsed or refractory disease and treatment selection depends on prior therapies, duration of response, residual toxicities and patient-related factors[21,30].

Evidence supports the use of triplet and quadruplet regimens combining proteasome inhibitors, immunomodulatory agents and monoclonal antibodies, which have demonstrated higher response rates and improved survival outcomes compared with doublet regimens. In selected patients who achieved durable responses after initial autologous stem cell transplantation, a second transplantation has been shown to provide additional disease control [21].

Supportive and local treatment modalities. Across the reviewed literature, supportive care emerged as a critical component of comprehensive multiple myeloma management. Antiresorptive therapies, including bisphosphonates and other bone-targeted agents, were shown to reduce skeletal-related events and improve pain control [29,41]. Because cancer-related pain has substantial physical and psychosocial consequences, systematic pain assessment and individualized multimodal management should be integrated into supportive care[44]. Radiotherapy remains an effective option for the management of focal bone pain, pathological fractures and spinal cord compression. In selected patients with recurrent pain following previous irradiation, palliative re-irradiation may provide additional pain relief while requiring careful consideration of cumulative toxicity[25–27,43]

Multidisciplinary approaches integrating systemic therapy, radiotherapy and selected orthopedic interventions were associated with improved functional outcomes and quality of life [8,41]. In addition, infection prevention, renal protection and management of treatment-related toxicities were consistently emphasized as essential elements of long-term care[4,20].

Treatment-related toxicities and patient fitness

The literature highlights a broad spectrum of adverse events associated with modern myeloma therapies, including hematologic toxicity, peripheral neuropathy, cardiovascular complications, thromboembolic events, infections and metabolic disturbances [2,4,17,33]. These toxicities were shown to have a significant impact on treatment adherence and quality of life, particularly in elderly and frail patients[4,32].

Assessment of patient fitness and frailty was identified as a key factor in optimizing treatment intensity and preventing early treatment discontinuation. Dose modification strategies and supportive interventions were commonly recommended to balance efficacy and tolerability[4,20].

Summary of evidence synthesis

Overall, the reviewed studies demonstrate that modern management of multiple myeloma is characterized by the widespread use of combination systemic therapies, risk-adapted treatment selection and increasing reliance on targeted agents[6,22,23,30]. Autologous stem cell transplantation continues to play a central role in eligible patients, while novel antibody-based regimens have expanded therapeutic options for transplant-ineligible and relapsed populations[10,11,22]. Supportive care and multidisciplinary management remain essential to achieving optimal clinical outcomes[8,29,41].

Discussion. The management of multiple myeloma has entered an era of unprecedented therapeutic complexity. The availability of multiple effective drug classes and combination regimens has significantly improved clinical outcomes but has also increased the challenge of selecting the most appropriate treatment strategy for individual patients. Risk-adapted therapy, integrating disease biology with patient-related factors, has therefore become a central principle of modern myeloma care.

For patients eligible for autologous stem cell transplantation, induction therapy incorporating proteasome inhibitors, immunomodulatory agents and corticosteroids remains the standard of care, often supplemented by anti-CD38 monoclonal antibodies. High-dose chemotherapy followed by transplantation continues to provide durable disease control and remains a cornerstone of treatment, particularly in younger and fit individuals[10,30]. However, the optimal timing of transplantation—upfront versus delayed until first relapse—remains an area of ongoing debate, especially in patients achieving deep responses with modern induction regimens.

In transplant-ineligible patients, less intensive but effective regimens are required to minimize toxicity while preserving efficacy. Combinations based on lenalidomide, bortezomib and anti-CD38 monoclonal antibodies have demonstrated favorable outcomes in this population, although treatment-related adverse events and cumulative toxicity remain important considerations[11,22]. Frailty assessment and careful dose adjustment are essential to prevent treatment discontinuation and preserve quality of life.

Relapsed and refractory multiple myeloma continues to pose a major therapeutic challenge. With each subsequent relapse, disease biology often becomes more aggressive and resistant to therapy. Triplet and quadruplet regimens incorporating proteasome inhibitors, immunomodulatory agents and monoclonal antibodies have improved response rates and survival outcomes, yet long-term disease control remains elusive for many patients [21,30]. Treatment selection in this setting must be individualized, taking into account prior therapies, duration of response, residual toxicities and patient preference.

Beyond systemic therapy, supportive and local treatment modalities play a critical role in comprehensive myeloma management[8,29]. The prevention and treatment of bone disease, infection, renal impairment and treatment-related toxicities are essential components of a multidisciplinary approach. Radiotherapy, antiresorptive agents and selected orthopedic interventions remain important adjuncts to systemic therapy, particularly in patients with skeletal-related events. Recent clinical evidence highlights the importance of early identification and multidisciplinary management of myeloma-related bone disease to reduce skeletal-related events and preserve functional outcomes [39,41]. Assessment of quality of life has emerged as a key component of modern myeloma management, providing essential information for treatment individualization and long-term patient care[42].

Despite significant progress, several unmet needs remain. Access to novel therapies varies across healthcare systems and treatment costs represent a growing concern. Furthermore, the integration of emerging strategies such as minimal residual disease–guided therapy, bispecific antibodies and cellular therapies is expected to further refine risk-adapted treatment algorithms in the coming years[16,30].

Integrative reviews and real-world data further support the application of risk-adapted systemic treatment

strategies across different healthcare settings [40]. In summary, contemporary management of multiple myeloma requires a personalized, risk-adapted approach that integrates disease biology, patient fitness and therapeutic goals. Continued refinement of treatment strategies and the incorporation of novel agents are expected to further improve long-term outcomes while maintaining quality of life.

CONCLUSIONS

The management of multiple myeloma has evolved considerably with the introduction of novel systemic therapies and the refinement of transplant-based strategies. Contemporary evidence supports a personalized, risk-adapted treatment approach that integrates disease biology, transplant eligibility and patient fitness to optimize clinical outcomes.

Combination regimens incorporating proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies represent the foundation of modern therapy across different disease stages. Autologous stem cell transplantation remains a key component of treatment for eligible patients, while effective and less intensive regimens are essential for elderly or frail individuals. In relapsed or refractory disease, sequential use of combination therapies continues to improve disease control, although long-term remission remains challenging.

Overall, risk-adapted systemic therapy, supported by comprehensive supportive care and multidisciplinary management, is central to improving survival and maintaining quality of life in patients with multiple myeloma. Ongoing advances in risk stratification and targeted therapies are expected to further refine treatment strategies and enhance long-term outcomes.

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Conflict of interest
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Availability of Data and Materials
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