



Recent Advances in the Treatment of Multiple Myeloma in the Era of New Drug Development

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Abstract

Multiple myeloma (MM) is a malignant hematologic disease characterized by the neoplastic proliferation of plasma cells in the bone marrow. It exhibits high heterogeneity, a tendency for relapse, and resistance to treatment. The primary goal of first-line therapy is to achieve deep remission and durable disease control. Current conventional treatment approaches can improve patient prognosis but have significant limitations. The emergence of novel therapies, including proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, chimeric antigen receptor T-cell therapy, and immune checkpoint inhibitors, marks a new era in MM treatment. However, due to the relapsed and refractory nature of MM, future applications should consider various factors and tailor treatment strategies to individual circumstances to optimize therapeutic efficacy.

Keywords

Multiple Myeloma, Immunotherapy, Proteasome Inhibitors, Immunomodulatory Agents, Monoclonal Antibodies, Chimeric Antigen Receptor T Cells, Immune Checkpoint Inhibitors

Introduction

Multiple myeloma (MM) is a malignant hematologic disorder characterized primarily by the neoplastic proliferation of plasma cells in the bone marrow [1]. The exact pathogenesis remains unclear; however, it is currently believed to be associated with genetic alterations, abnormalities in cell signaling pathways, and changes in the bone marrow microenvironment. Clinical manifestations primarily include anemia, renal impairment, hypercalcemia, and bone pain [2]. MM is quite prevalent among hematologic tumors, with data indicating that it accounts for over 10% of all hematologic malignancies [3]. MM is highly

heterogeneous, resulting in significant variability in patient prognosis, yet the five-year survival rate remains only 50%. Current treatment approaches for MM mainly involve chemotherapy and hematopoietic stem cell transplantation, which can improve patient outcomes and prolong survival. However, clinical applications are often limited due to factors such as drug resistance, adverse reactions, high relapse rates post-remission, as well as risks associated with transplant infections and the long-term use of postoperative immunosuppressants. Additionally, the presence of drug resistance and immune evasion ultimately leads to the development of relapsed and

refractory multiple myeloma (RRMM) in patients [4]. Therefore, extending survival and improving the quality of life for MM patients remain central focuses of current treatment strategies.

In recent years, an increased understanding of the bone marrow microenvironment and the pathogenesis of MM has prompted exploration into the application of immunotherapy in its treatment [5,6]. The advent of next-generation proteasome inhibitors (PIs), immunomodulatory imide drugs (IMiDs), monoclonal antibodies, chimeric antigen receptor T-cell (CAR-T) therapy, and immune checkpoint inhibitors has introduced new strategies for MM treatment, making these agents a research hotspot in antitumor therapy for MM. This article provides a review of recent advances in novel drug therapies for MM.

Traditional Treatment Approaches for Multiple Myeloma

Chemotherapy and Radiotherapy:

Currently, the treatment of multiple myeloma (MM) primarily involves combination chemotherapy, with regimens such as VTD (bortezomib, thalidomide, dexamethasone) and RVD (lenalidomide, bortezomib, and dexamethasone) demonstrating significant clinical efficacy. Dong et al. [7] reported a case of MM coexisting with non-small cell lung cancer, where the patient achieved good therapeutic outcomes following treatment with the VDT regimen, and adverse reactions were effectively managed. This case provides new insights into the combined treatment of MM.

Due to the dissemination and metastasis of myeloma cells in MM patients, radiotherapy is not considered a first-line treatment option. Instead, it is primarily used as an adjunctive therapy to alleviate symptoms such as bone pain and spinal cord compression [8,9]. Research by Zijlstra et al. [10] indicated that MM patients with spinal cord compression who underwent surgical treatment exhibited better recovery of neurological function and pain relief compared to those who received radiotherapy alone. However, there were no significant differences in the need for relapse treatment or other adverse reactions between the two groups.

The fundamental principle of radiotherapy is to

induce apoptosis in cells through radiation exposure, which inevitably results in some damage to normal human cells. The side effects primarily include damage to the skin, mucous membranes, and gastrointestinal and hematopoietic systems [11]. Zijlstra et al. [10] also found that MM patients receiving radiotherapy frequently experienced gastrointestinal reactions, skin and mucosal damage, and leukopenia; however, these adverse effects did not significantly increase the risk of relapse or mortality compared to surgical treatment. Guerini et al. [12] conducted a retrospective analysis of 312 MM patients who underwent radiotherapy and found that, although concomitant systemic treatment (CST) and high biologically effective dose (BED 10) radiotherapy were associated with higher toxicity risks, the overall safety was satisfactory, with a rate of ≥ 2 grade adverse reactions at only 4.1%. Moreover, radiotherapy significantly improved pain control, with a pain relief rate of 87.4% at the end of treatment, which increased to 96.9% at three months.

Hematopoietic Stem Cell Transplantation:

Hematopoietic stem cell transplantation (HSCT) is the preferred option for newly diagnosed MM patients following induction therapy. Patients suitable for transplantation are typically recommended this treatment to alleviate their condition [13]. Early stem cell mobilization strategies primarily relied on the use of granulocyte colony-stimulating factor (G-CSF). However, with the introduction of plerixafor, the combination of G-CSF and plerixafor has significantly improved the success rate of stem cell mobilization, while also reducing adverse reactions and shortening hospital stays [14]. HSCT has also demonstrated favorable efficacy in patients with relapsed MM [15], although the suitability for transplantation depends on the patient's age and organ function [16]. The 2020 edition of the "Chinese Guidelines for the Diagnosis and Treatment of Multiple Myeloma" has adjusted the upper age limit for transplantation, recommending this therapy for elderly patients in good health, further underscoring the importance of HSCT in the treatment of MM.

Several studies have identified the primary complications associated with HSCT in MM patients, including neutropenia with subsequent infection, liver

dysfunction, thrombocytopenia, anemia, oral mucositis, and gastrointestinal discomfort [17–18]. Early identification and management of risk factors for transplantation-related adverse reactions are crucial for reducing transplant-related complications.

Novel Drug Therapies for Multiple Myeloma

Proteasome Inhibitors (PIs):

Currently, the commonly used proteasome inhibitors (PIs) in clinical practice include bortezomib, carfilzomib, and ixazomib. Bortezomib, a first-generation PI belonging to the boronic acid peptide class, has high selectivity and reversibly binds to the proteasome. Studies have shown that the combination of bortezomib and dexamethasone can enhance treatment efficacy, increase immune cell levels, reduce the secretion of immunosuppressive factors, and mitigate bone damage [19]. Despite its favorable clinical outcomes, bortezomib is associated with adverse effects such as thrombocytopenia, neutropenia, and neuropathy [20]. Notably, 30% to 60% of patients may experience peripheral neuropathy, which may be related to endoplasmic reticulum stress and inflammatory responses.

Carfilzomib, a second-generation PI classified as an epoxyketone, differs from bortezomib by irreversibly binding to the proteasome, resulting in a more potent inhibitory effect. Carfilzomib has a lower incidence of neurotoxicity, better patient tolerability, and high safety, making it suitable for long-term use [21]. An age stratification analysis by Dimopoulos et al. [22], based on the ASPIRE phase III clinical trial, found that in MM patients over 70 years old, the combination of carfilzomib with lenalidomide and dexamethasone significantly prolonged progression-free survival and overall survival compared to lenalidomide and dexamethasone alone. Adverse reactions primarily included pneumonia, heart failure, and anemia, with a low incidence of peripheral neuropathy (13.9%), although cardiovascular adverse events were relatively high [5,6].

Ixazomib is the first oral proteasome inhibitor globally. Stege et al. [23] applied a regimen of ixazomib, daratumumab, and low-dose dexamethasone in 143 newly diagnosed MM patients, reporting an overall

response rate of 78% in elderly frail patients, with a median progression-free survival of 13.8 months and a 12-month overall survival rate of 78%. Only 9% of patients discontinued treatment due to adverse reactions, indicating that this regimen is both effective and well-tolerated in elderly MM patients.

Although PI therapy shows significant efficacy in treating MM, myeloma cells are prone to develop primary and acquired resistance. The mechanisms of resistance primarily involve the ubiquitin-proteasome system, endoplasmic reticulum stress, autophagy, genetic mutations, and the bone marrow microenvironment [21,22]. Relapses caused by resistance are a major cause of mortality in MM patients. Therefore, delaying and overcoming resistance is a critical issue in the clinical application of PIs. Current research focuses on overcoming PI resistance through the combined use of agents targeting different mechanisms.

Immunomodulatory Drugs (IMiDs):

IMiDs in clinical practice include thalidomide, lenalidomide, and pomalidomide. These drugs share similar mechanisms of action, such as anti-angiogenesis, immune modulation, and cytotoxicity [24]. Numerous studies have shown that the application of immunomodulatory agents in MM patients extends progression-free survival and improves quality of life. The Cereblon gene, located on chromosome 3, is a binding protein that was initially identified due to the teratogenic effects of thalidomide [25]. Further research has demonstrated that Cereblon can form complexes with DNA damage-binding proteins, CUL4, and regulatory factors, promoting the ubiquitination of downstream target proteins, which are subsequently degraded by the proteasome [26]. Zinc finger protein 1 and zinc finger protein 3 play significant roles in lymphocyte proliferation and differentiation. Thalidomide and other immunomodulatory agents enhance the activity of these complexes by binding to Cereblon, promoting the degradation of zinc finger proteins, and thereby exerting a cytotoxic effect on myeloma cells. However, due to the peripheral neuropathy and other adverse reactions associated with thalidomide, its clinical use requires caution.

Lenalidomide is a second-generation analog of thalidomide, exhibiting greater potency and fewer adverse effects, primarily used in newly diagnosed MM. Research has demonstrated that the combination of bortezomib, lenalidomide, and dexamethasone is an effective induction regimen for both transplant-eligible and non-transplant-eligible patients, and it is recommended as a first-line treatment in the NCCN guidelines [27]. The combination of lenalidomide and carfilzomib is increasingly used for the induction treatment of high-risk MM patients [28], with low-dose regimens showing favorable efficacy in elderly MM patients [29]. Multiple studies indicate that lenalidomide significantly improves progression-free survival and overall survival in MM patients [30].

Pomalidomide, another analog of thalidomide, was approved by the FDA in 2013 for use in combination with dexamethasone for the second-line treatment of relapsed or refractory MM patients who have previously received bortezomib or lenalidomide [31]. Several clinical trials have confirmed the efficacy of this regimen. A recent study demonstrated that among 106 patients who received at least two cycles of pomalidomide combined with dexamethasone, the overall response rate was 43.3%, with a median progression-free survival of 8.5 months and an overall survival of 14 months, further validating the efficacy of this regimen in relapsed/refractory MM patients [31].

Monoclonal Antibodies:

Daratumumab, widely utilized in clinical practice, is a fully humanized anti-CD38 monoclonal antibody that exerts its therapeutic effects by binding to CD38 expressed on myeloma cells, thereby mediating antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) to specifically eliminate myeloma cells. Additionally, daratumumab depletes CD38-positive regulatory T cells, promotes polyclonal T cell expansion, and enhances interferon- γ secretion capacity [32]. The efficacy of daratumumab in patients with relapsed/refractory multiple myeloma (RRMM) has been extensively validated [33]. Recent studies have demonstrated that combining daratumumab with immunomodulatory drugs and proteasome inhibitors can improve response rates and extend progression-

free survival (PFS) in newly diagnosed elderly MM patients.

A multicenter, open-label, randomized phase III clinical trial involving 737 patients demonstrated that the combination of daratumumab with lenalidomide and dexamethasone significantly prolonged progression-free survival compared to lenalidomide and dexamethasone alone, while maintaining favorable safety and efficacy profiles even in frail MM patients [34]. Another study encompassing 706 transplant-ineligible MM patients [35] compared daratumumab in combination with bortezomib, melphalan, and dexamethasone versus the latter regimen without daratumumab. The combination therapy group achieved higher complete response rates without significantly increasing grade 3-4 adverse events. Currently, the combination of daratumumab with bortezomib, melphalan, and dexamethasone has emerged as the preferred treatment protocol for newly diagnosed elderly MM patients.

Furthermore, other FDA-approved monoclonal antibodies include elotuzumab (anti-CD319) and isatuximab (Sarclisa) for RRMM treatment. While elotuzumab demonstrates limited efficacy as monotherapy, its therapeutic potential is significantly enhanced when combined with lenalidomide or pomalidomide [36]. Similarly, isatuximab in combination with carfilzomib and dexamethasone substantially extends progression-free survival in RRMM patients. However, immune escape due to antigenic epitope internalization or loss in RRMM cells remains a primary cause of treatment failure with monoclonal antibodies [37]. Future directions in this field may focus on optimizing existing antibodies or developing novel targeted approaches.

CAR-T Therapy:

CAR-T cell therapy is a form of gene-modified cellular treatment. Given that MM tumor cells consistently express B-cell maturation antigen (BCMA), CAR-T therapies designed to target BCMA have demonstrated promising clinical efficacy. Yang Xu et al. [38] evaluated the efficacy of CD27-modified BCMA CAR-T cell therapy (CBG-002) in a phase I clinical trial involving patients with relapsed and refractory multiple myeloma

(RRMM). The results indicated an overall response rate of 81.8%, with 45.5% of patients achieving stringent complete response or complete response. In phase II trials, the response rate in patients with refractory or relapsed MM reached as high as 95%. A domestic phase I clinical study showed that the overall response rate for RRMM patients receiving BCMA CAR-T therapy was 87.5%, with a median progression-free survival of 18.8 months [39]. However, the relatively high rate of relapse remains a significant challenge for BCMA CAR-T therapy. The mechanisms underlying the relapse of MM after CAR-T treatment are not yet fully understood and may be related to the poor persistence of CAR-T cells in vivo, antigen escape, and changes in the bone marrow microenvironment [40].

Qi Yuekui et al. [41] found that while CAR-T therapy has some efficacy in patients with relapsed/refractory MM with extramedullary disease (EMD), the duration of response shortens over time, and concerns regarding long-term efficacy and safety remain. Future efforts should focus on targeting additional antigens in CAR-T therapy and enhancing the persistence of CAR-T cells to optimize therapeutic outcomes.

Immune Checkpoint Inhibitors:

Mechanisms and Clinical Trial Results of PD-1/PD-L1 Inhibitors:

Programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) are widely recognized as negative regulatory pathways within the body. PD-1 is primarily expressed on T cells, cells in the bone marrow microenvironment, and B cells, while PD-L1 is predominantly expressed on antigen-presenting cells [42]. Under normal conditions, PD-L1 is expressed at low levels in normal cells and tissues; its binding to PD-1 inhibits the excessive activation of immune cells, thereby preventing damage to normal tissues [43]. However, studies have shown that in various tumors, cancer cells often exhibit high levels of PD-L1 expression, leading to excessive suppression of immune cell function upon binding with PD-1, resulting in immune evasion. PD-1/PD-L1 inhibitors work by blocking the interaction between PD-1 and PD-L1, thereby restoring the normal cytotoxic function of immune cells, which constitutes their primary mechanism of action.

Nevertheless, the efficacy of PD-1 monoclonal antibodies in the treatment of multiple myeloma (MM) has been generally suboptimal [44]. Research by De Veirman et al. [42] demonstrated that using an 225Ac-labeled CS1-specific single-domain antibody in a mouse model of MM exhibited favorable therapeutic effects, significantly extending survival and increasing the number of CD8⁺ T cells while enhancing PD-L1 expression. This study suggests that CS1-targeted radionuclide therapy (TRNT) not only possesses therapeutic efficacy but also exhibits immune modulatory effects, providing a new potential avenue for the treatment of MM.

Mechanisms and Clinical Trial Results of CTLA-4 Inhibitors:

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors function similarly to PD-1/PD-L1 inhibitors. CTLA-4 is primarily expressed on T cells and binds to CD80/86 on antigen-presenting cells, inhibiting the excessive activation of T cells and thereby facilitating immune evasion by tumor cells. CTLA-4 inhibitors block this binding, reactivating T cells to kill tumor cells, thereby achieving therapeutic effects against tumors.

One notable CTLA-4 inhibitor is ipilimumab, which has been approved for the treatment of melanoma and has shown significant efficacy [45,46]. However, clinical research on its application in multiple myeloma (MM) is relatively limited [47].

Currently, there is sparse research on the use of immune checkpoint inhibitors in MM. Available studies indicate that these inhibitors are associated with adverse effects, including skin toxicity, gastrointestinal reactions, liver damage, pneumonia, and cardiovascular injury [48-52]. While the emergence of immune inhibitors provides new avenues for the treatment of MM, their clinical application still requires robust data to support efficacy and safety.

Outlook

In recent years, new-generation proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, chimeric antigen receptor T-cell therapy, and immune checkpoint inhibitors have gradually

gained attention, with patients generally reporting good clinical outcomes. However, issues regarding drug resistance and safety remain contentious. As MM is a highly heterogeneous disease, a single treatment modality tends to have limited efficacy. Ongoing research into MM is expanding the range of treatment options, demonstrating significant potential. Future developments may include new-target combination therapies that integrate various immunotherapies, as well as novel drug combinations with traditional treatment methods, which could become key strategies in MM management.

Nonetheless, the treatment landscape for MM remains fraught with uncertainties and challenges. Future efforts should focus on multi-center, high-quality clinical trials to address key issues such as the selection of immunotherapy types, combinations of different immunotherapies, optimal treatment sequences, and the best timing for intervention, ultimately aiming to provide more rational and effective treatment options for MM patients.

Author Contributions

Bing Xiang, Qing Hu—designed the research study.
Qing Hu—performed the research.
Qing Hu—analyzed the data.
Qing Hu and Bing Xiang—wrote the manuscript.
All authors read and approved the final manuscript.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

Ethics

The study protocol was reviewed and approved by the Ethical Committee of the West China Hospital. All experiments were performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from all patients.

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