

Stadnik Y.O., Maslova G.S.

Poltava State Medical University, Poltava, Ukraine

CONTEMPORARY THERAPEUTIC APPROACHES FOR MULTIPLE MYELOMA

e-mail: ye.stadnik@pdmu.edu.ua

This review article analyzes contemporary therapeutic approaches for patients with multiple myeloma. The literature selection was conducted within the Pubmed and Google Scholar databases, encompassing publications from the period of 2020 to 2025. A fundamental principle in the management of multiple myeloma patients is the initial determination of eligibility for autologous hematopoietic stem cell transplantation. Performing autologous hematopoietic stem cell transplantation increases the rate of clinico-hematological remission achievement and improves patient survival outcomes. The development and implementation of novel therapeutic approaches remains a critical focus. Furthermore, enrolling patients in clinical trials is essential, particularly for those with relapsed/refractory multiple myeloma and patients with high-risk disease features. An ongoing area of significant importance is the investigation of supportive care strategies, particularly agents for bone remodeling. This is critically important for improving patient quality of life and reducing the risk of skeletal-related complications.

Key words: multiple myeloma, chemotherapy, treatment, autologous hematopoietic stem cell transplantation, proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies.

Стаднік Є.О., Маслова Г.С.

СУЧАСНІ ТЕРАПЕВТИЧНІ ПІДХОДИ ДО ЛІКУВАННЯ МНОЖИННОЇ МІЄЛОМИ

Оглядова стаття присвячена аналізу сучасних підходів до лікування хворих на множинну мієлому. Відбір літератури проведено в базах даних Pubmed та Google Scholar, опублікованих у період з 2020 по 2025 роки. Основним принципом лікування хворих на мієлому є первинне визначення кандидатів для проведення аутологічної трансплантації стовбурових клітин, проведення якої дозволяє підвищити частоту досягнення клініко-гематологічних ремісій та покращити показники виживаності пацієнтів. Важливим напрямом залишається розробка та впровадження нових терапевтичних підходів, а також залучення пацієнтів до клінічних досліджень, особливо для осіб із рецидивною/рефрактерною множинною мієломою та пацієнтів із високим ризиком прогресування захворювання. Актуальною проблемою залишається дослідження супутньої терапії, зокрема засобів для ремоделювання кісткової тканини, що є критично важливим для підвищення якості життя пацієнтів і зниження ризику ускладнень.

Ключові слова: множинна мієлома, хіміотерапія, лікування, аутологічна трансплантація гемопоетичних стовбурових клітин, інгібітори протеасом, імуномодуючі препарати, моноклональні антитіла.

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Multiple myeloma (MM) is a malignant plasma cell disorder associated with bone marrow infiltration and paraproteinemia. It is characterized by clinical features such as anemia, hypercalcemia, renal insufficiency, osteolytic bone lesions, and immunodeficiency with recurrent infections [2, 12, 19, 24, 26]. MM is the second most common hematologic malignancy, accounting for approximately 10% of all cases [10, 18, 19, 26]. The incidence of MM increases with age, with a median age at diagnosis of 65-69 years [17, 24, 26]. The annual incidence ranges from 4.5 to 6 cases per 100,000 individuals [6, 19].

The pathogenesis of MM is driven by a complex interplay between genetic abnormalities and the bone marrow microenvironment, within which MM cells interact with various cellular and molecular components [19, 24]. These interactions trigger the activation of numerous intracellular signaling pathways, which ultimately promote tumor cell growth, survival, and migration. Key signaling pathways implicated in MM pathogenesis include PI3K/AKT/mTOR, RAS/MAPK, JAK/STAT, Wnt/ β -catenin, and NF- κ B [19]. Mutations in the KRAS and NRAS genes can activate the MAPK/ERK signaling pathway, stimulating cell growth and

survival. Loss of function of the TP53 tumor suppressor gene or the presence of mutations in this gene is associated with a poor prognosis and therapy resistance. Dysregulation of the Wnt signaling pathway and the overexpression of DKK1 activate osteoclasts, leading to the development of osteolytic lesions in multiple myeloma [19, 24]. Targeting these signaling pathways using inhibitors and inducers represents a promising therapeutic strategy for MM [19].

Survival outcomes in patients with MM vary depending on the data source. Published clinical observations indicate that in patients who are candidates for transplantation, overall survival (OS) exceeds 10 years. In patients over 75 years of age, the median OS is approximately 5 years. However, these estimates may be conservative, as they are based on data analyzed prior to the introduction of monoclonal antibodies and other innovative agents [26]. The use of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies (mAbs), and the administration of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) have significantly improved treatment response rates and increased survival outcomes [13, 24].

Staging is performed using the Durie-Salmon and International Staging System (ISS) classifications. The revised R-ISS (Revised ISS) has augmented the original ISS, which only incorporated serum albumin and β 2-microglobulin levels, by adding cytogenetic risk factors and serum lactate dehydrogenase (LDH) levels [10].

The presence of del(17p), t(4;14), t(14;16), t(14;20), amp(1q), del(1p), or TP53 gene mutation is classified as high-risk MM [10, 26]. The co-occurrence of two of these abnormalities indicates so-called "double-hit" myeloma, while the presence of three or more risk factors defines "triple-hit" myeloma [26].

In some cases, myeloma cells can migrate beyond the bone marrow, leading to the development of an extramedullary form of the disease – extramedullary multiple myeloma (EMM). It can arise either at the time of initial MM diagnosis (primary EMM) or during disease relapse (secondary EMM). EMM represents a distinct clinical subgroup that is generally associated with a significantly poorer prognosis due to resistance to standard therapeutic approaches, particularly in cases of secondary EMM [2].

A key refinement in the response assessment criteria has been the introduction of Minimal Residual Disease (MRD) evaluation. MRD can be detected both within the bone marrow using next-generation sequencing or flow cytometry, and extramedullarily via positron emission tomography-computed tomography (PET-CT) [7].

Achieving an MRD-negative status in the bone marrow of patients who have attained a complete response is consistently associated with longer progression-free survival (PFS) and OS. This correlation holds true for both patients with newly diagnosed MM and those with relapsed/refractory MM (RRMM) [6, 7, 9, 24].

PET-CT detects hypermetabolic lesions in approximately 15-20% of patients with an MRD-negative status in the bone marrow and is currently considered the most effective imaging modality [7]. Furthermore, focal lesions identified by PET-CT have prognostic significance: the presence of more than three PET-positive lesions is associated with inferior OS and median PFS, whereas PET normalization following therapy is correlated with improved treatment outcomes [12].

Current research is investigating the feasibility of discontinuing maintenance or continuous therapy in patients with sustained MRD negativity, as well as the necessity of treatment modification in MRD-positive patients, particularly in cases of high-risk MM [7].

In patients with high-risk MM, both PFS and median OS are lower than in those with standard-risk disease. Prognosis is also influenced by the patient's performance status, disease stage at diagnosis, cytogenetic abnormalities, and depth of response to therapy [10].

The purpose of the study was to systematize current data concerning contemporary therapeutic approaches to MM, including ASCT, novel treatment strategies, and supportive care aimed at improving survival outcomes and quality of life in patients with MM.

Materials and methods. This literature review included studies reporting on contemporary therapeutic approaches to MM, including ASCT, PIs, IMiDs, mAbs, novel treatment strategies, and supportive care. The literature search was conducted in the Pubmed and Google Scholar databases and included publications from 2020 to 2025. The last search query was performed on September 9, 2025. As a result, 30 publications in English were selected, confirming the adequacy of the information for conducting a systematic review and achieving the purpose of the analysis.

To ensure comprehensive coverage of the research, we used the following search strategy:

Database 1 – PubMed. Search query (verbatim): ("multiple myeloma" OR "newly diagnosed multiple myeloma" OR "relapsed multiple myeloma" OR "refractory multiple myeloma" OR "relapsed/refractory multiple myeloma" OR "high-risk multiple myeloma") AND ("treatment" OR "therapy" OR "chemotherapy" OR "therapeutic approaches") AND ("autologous hematopoietic stem cell transplantation" OR "ASCT" OR "proteasome inhibitors" OR "immunomodulatory drugs" OR "monoclonal antibodies" OR "CAR-T cell therapy").

Database 2 – Google Scholar. Search query (verbatim): "multiple myeloma" AND ("treatment" OR "therapy" OR "chemotherapy" OR "therapeutic approaches") AND ("autologous hematopoietic stem cell transplantation" OR "ASCT" OR "proteasome inhibitors" OR "immunomodulatory drugs" OR "monoclonal antibodies" OR "supportive care" OR "prophylaxis of chemotherapy-induced liver injury").

The review methodology was developed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The selected data were synthesized using comparative and trend analysis to identify current patterns and recent developments in multiple myeloma treatment. Conference abstracts, editorials, preprints, non-peer-reviewed publications, and studies that did not provide sufficient relevant data on therapeutic approaches to multiple myeloma were excluded from the analysis.

Results of the study and their discussion. In the early stages, the management of MM was predominantly palliative. The therapeutic strategy was aimed at alleviating symptoms, such as bone pain and hypercalcemia. The primary treatment modalities involved radiation therapy and high-dose corticosteroids, which provided temporary symptomatic improvement but had no impact on OS. The introduction of combination therapy with melphalan and prednisolone in the 1960s represented

a significant breakthrough, enabling more durable responses and improved survival. This established the melphalan and prednisolone regimen as the standard of care for many years [9].

According to contemporary treatment standards, the therapeutic approach for MM patients is contingent upon their eligibility for ASCT [6, 9, 14, 26]. The standard of care remains the administration of ASCT following induction therapy in the early phases for transplant-eligible patients [6, 24, 28]. Concurrently, there is an increasing convergence in induction therapy strategies for both transplant-eligible patients and those for whom transplantation is not indicated [14]. Stem cell harvesting is performed after 3-4 cycles of induction therapy, followed by immediate transplantation, or chemotherapy is continued until disease relapse, at which point delayed ASCT is performed [10, 26]. The administration of ASCT improves the median OS in MM by approximately 12 months [26]. However, randomized controlled trials consistently demonstrate comparable OS with early ASCT (immediately after 4 cycles of induction therapy) compared to delayed ASCT. According to current research, early ASCT provides superior PFS compared to transplantation deferred until relapse, but without a significant difference in overall survival [24, 26]. The US-based DETERMINATION trial also failed to demonstrate an advantage for early ASCT. Consequently, delayed ASCT is an acceptable option, particularly for patients with standard-risk myeloma who opt for this approach due to personal or logistical considerations [26].

The primary contraindications to ASCT include poor performance status, liver cirrhosis, and heart failure (New York Heart Association functional class III-IV). However, a significant number of patients who are potential candidates for transplantation are never referred to ASCT centers for evaluation [14].

Recent advances in immunotherapy, particularly chimeric antigen receptor T-cell therapy (CAR T-cell therapy) and bispecific antibodies, are unveiling promising novel modalities with the potential to transform the therapeutic landscape of myeloma, especially for patients who are ineligible for ASCT [9].

Allogeneic transplantation is currently considered only within the context of clinical trials [10].

The management of MM typically consists of several phases: induction therapy, consolidation, and maintenance therapy [6, 24].

Beyond primary anti-myeloma treatment, the administration of supportive care remains a critical component of management. These measures include analgesia, prophylaxis against infections and thrombosis, reduction of the risk of pathological fractures, and the management of other disease-related symptoms. MM therapy is aimed at achieving a durable and deep response while minimizing

treatment-related toxicity and improving patients' quality of life [24].

Over the past two decades, the introduction of IMiDs, PIs, and mAbs has significantly transformed MM treatment paradigms [3, 14, 23, 28]. The initial agents that improved treatment response rates were thalidomide, lenalidomide, and bortezomib [26].

Bortezomib was the first-in-class proteasome inhibitor (PI) and contributed to improved outcomes for MM patients; it is now widely utilized in various therapeutic regimens [3].

Therefore, from our perspective, it is pertinent to delineate the following strategic directions in the management of MM patients:

1. Management of transplant-eligible patients.
2. Management of transplant-ineligible patients.
3. Maintenance therapy.
4. Treatment of RRMM.
5. Contemporary approaches to supportive care in MM.

Management of Transplant-Eligible Patients. According to current European guidelines, ASCT is recommended for patients up to 70 years of age, whereas guidelines from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology do not impose a strict age limit [4, 26].

The current standard of care for this patient group is induction therapy consisting of lenalidomide, a PI (bortezomib or carfilzomib), and dexamethasone [10, 14, 24]. For high-risk patients, four-drug regimens containing a mAb are preferred [10].

Bortezomib was the first PI to receive approval from the United States Food and Drug Administration (FDA) in 2003 [28].

The use of the VRD regimen (bortezomib, lenalidomide, dexamethasone) is supported by data from the phase III SWOG S0777 clinical trial. In long-term follow-up, which included 460 patients with a median follow-up of 84 months, the median PFS was 41 months for VRD compared to 29 months for RD (lenalidomide, dexamethasone) [24]. The VRD regimen has become the standard of care for newly diagnosed MM (NDMM), irrespective of age [24, 28].

In the absence of lenalidomide or in cases of acute renal failure, alternative bortezomib-based regimens may be used. One such regimen is Dara-VCD (daratumumab, bortezomib, cyclophosphamide, dexamethasone) [26].

The ENDURANCE trial compared the efficacy of the KRD (carfilzomib, lenalidomide, dexamethasone) and VRD regimens. The study results demonstrated no difference in PFS [14, 24]. However, the administration of KRD was associated with a higher incidence of grade III/IV toxicities [24]. It is noteworthy that the trial only included standard-risk patients, as it excluded individuals with del(17p), t(4;14), t(14;16), t(14;20), plasma cell leukemia, or a

LDH level more than twice the upper limit of normal [14, 24]. A direct comparison of the VRD and KRD regimens followed by ASCT has not been conducted [14].

In the FORTE trial, an evaluation was conducted to assess the safety and efficacy of the following treatment regimens: KRD followed by ASCT and KRD consolidation (KRD-ASCT-KRD) compared to 12 cycles of KRD (KRD12), as well as the regimen of KCD (carfilzomib, cyclophosphamide, dexamethasone) induction followed by ASCT and KCD consolidation (KCD-ASCT-KCD) [28]. The study results demonstrated that therapy with KRD followed by ASCT was superior to both the KRD regimen without ASCT and the KCD-based protocol. Furthermore, maintenance therapy with carfilzomib and lenalidomide was shown to improve PFS compared to lenalidomide alone [24, 28].

A key remaining area of investigation is the role of mAbs in combination with induction regimens. Data from the CASSIOPEIA and GRIFFIN trials support the efficacy of adding daratumumab to standard-of-care regimens. However, further research with longer follow-up is required to confirm the long-term benefits of this approach [1, 18, 24, 28].

Daratumumab, a mAb targeting CD38, has been established as a cornerstone of MM therapy. The recent expansion of its approved indications allows for the use of this first-in-class humanized mAb not only in RRMM but also in NDMM, irrespective of a patient's transplant eligibility [18, 26, 28].

The CASSIOPEIA trial enrolled 1085 patients who were randomized to receive either Dara-VTD (daratumumab, bortezomib, thalidomide, dexamethasone) or VTD (bortezomib, thalidomide, dexamethasone). On day 100 post-transplant, a stringent complete response (sCR) was achieved by 29% of patients in the Dara-VTD group, compared to 20% in the VTD group. Furthermore, undetectable MRD was recorded in 64% versus 44% of patients, respectively [18, 24].

The GRIFFIN study included 207 patients who were randomized to either Dara-VRD (daratumumab, bortezomib, lenalidomide, dexamethasone) or VRD. The regimen consisted of 4 cycles of induction therapy, followed by ASCT, 2 cycles of Dara-VRD or VRD consolidation, and maintenance therapy with lenalidomide plus daratumumab or lenalidomide alone (for 26 cycles). The sCR rate at the end of consolidation was 42.4% in the Dara-VRD group versus 32.0% in the VRD group. With a median follow-up of 22.1 months, the sCR rate deepened to 62.6% for Dara-VRD compared to 45.4% for VRD. The MRD-negativity rate was 51.0% for Dara-VRD versus 20.4% for VRD. The 24-month PFS was 95.8% in the Dara-VRD group, compared to 89.8% in the VRD group. It is important to note that a greater number of patients in the VRD control arm

discontinued the study at an early stage (<6 months after initiation), which was likely attributable to dissatisfaction with the treatment randomization [18, 24].

The combination of isatuximab with VRD (Isa-VRD) has also demonstrated impressive efficacy in the treatment of NDMM. The choice between the two quadruplet regimens, Dara-VRD and Isa-VRD, may be determined by their availability [26].

In addition to the aforementioned combinations, anthracycline-based regimens such as PAD (bortezomib, doxorubicin, dexamethasone) are utilized, along with multi-agent combination chemotherapy protocols, for example, VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide). These regimens are particularly relevant for patients with aggressive disease manifestations, such as plasma cell leukemia or multiple extramedullary plasmacytomas [26].

Consolidation therapy is a short-term treatment, typically involving two or more agents, administered prior to initiating long-term maintenance therapy. However, its use following ASCT is generally not recommended outside of clinical trials, and the majority of patients should transition directly to standard, low-intensity maintenance therapy [26].

Management of transplant-ineligible patients. For this patient group, from the late 1950s to the early 2000s, MM was associated with high early mortality and minimal therapeutic progress [4].

Patients with NDMM who are not candidates for ASCT have several main options for initial therapy: VRD or DRD (daratumumab, lenalidomide, dexamethasone) for frail patients, as well as Dara-VRD or Isa-VRD for patients with adequate performance status [26].

The VRD combination is typically administered for 8-12 cycles, after which patients transition to maintenance therapy. In contrast, DRD therapy involves the continuous administration of all three agents until disease progression, which significantly increases its long-term cost [26].

The results of the phase 3 MAIA clinical trial formed the basis for the approval of DRD in patients with NDMM who are not candidates for ASCT. In turn, the ALCYONE trial demonstrated that in transplant-ineligible patients with NDMM, treatment with the D-VMP regimen (daratumumab, bortezomib, melphalan, prednisolone) provides a significant improvement in PFS and OS compared to the VMP (bortezomib, melphalan, prednisolone) regimen without daratumumab [21, 24, 28].

If initial therapy with DRD or VRD is not feasible, for example due to logistical challenges (including issues with regimen adherence necessitated by the requirement for parenteral administration), regimens containing ixazomib may be substituted for bortezomib [26].

In cases of limited access to lenalidomide and anti-CD38 mAbs, VCD can be considered as an alternative [26].

Melphalan-containing regimens are not recommended [26].

For high-risk patients, the primary goal is to achieve and maintain a maximal response using first-line triple or quadruplet therapy that includes an anti-CD38 mAb, provided it is tolerable [4].

Principles of Maintenance Therapy. Maintenance therapy is recommended following ASCT. Furthermore, it should be considered for patients who have not undergone ASCT, upon completion of 8-12 cycles of induction therapy [26].

Lenalidomide is widely used as maintenance therapy [6, 24, 26]. Although lenalidomide is the preferred option for maintenance, in cases of its intolerance or contraindication, bortezomib or ixazomib may be considered [6, 28].

Ixazomib is the first oral PI [8, 27, 28]. The TOURMALINE-MM3 trial demonstrated that maintenance therapy with ixazomib prolongs PFS in patients post-ASCT compared to placebo. The TOURMALINE-MM4 study showed that the use of ixazomib for maintenance therapy following induction in patients with NDMM who did not undergo ASCT reduced the risk of progression or death by 34.1% compared to placebo [8, 28].

Treatment of RRMM. Despite significant advances in the treatment of MM, most patients will eventually experience disease relapse with resistance to conventional therapies [1, 23, 26]. Patients who achieved a long remission following their first transplant (exceeding 36 months) or those who did not undergo ASCT initially, should be considered for a delayed ASCT procedure. In the case of RRMM, an individualized approach to treatment selection is preferred [24]. The choice of therapeutic strategy is typically dependent on the prior line of therapy and the response to it, resistance to specific drug classes, and the patient's overall fitness status. Lenalidomide-based regimens are often preferred; however, in cases of resistance to this agent, alternative approaches are considered. These may include switching to a PI, utilizing novel agents such as pomalidomide, or employing innovative modalities, specifically mAbs and CAR T-cell therapy [13, 24]. Regarding pharmacotherapy, triple-drug regimens incorporating two novel agents to which the patient is not refractory are preferred [26].

Over the past decade, the following agents have been approved for the treatment of RRMM: carfilzomib, pomalidomide, ixazomib, elotuzumab, daratumumab, isatuximab, selinexor, belantamab mafodotin, teclistamab, talquetamab, and elranatamab, as well as CAR T-cell therapy, which have collectively significantly improved treatment outcomes [26].

PIs play a pivotal role in the treatment of RRMM [28]. Findings from the ENDEAVOR trial

established that the carfilzomib-dexamethasone combination improves both PFS and OS compared to bortezomib-dexamethasone in patients with RRMM. The ASPIRE study demonstrated that adding carfilzomib to lenalidomide-dexamethasone significantly enhances PFS and OS [28]. The TOURMALINE-MM1 trial determined that the inclusion of ixazomib to lenalidomide-dexamethasone significantly prolongs PFS, although it did not demonstrate a statistically significant improvement in OS [27, 28].

Bortezomib-based regimens are indicated for patients who experienced a long remission period following prior treatment with bortezomib-containing triple-drug regimens. VRD, VCD, and VTD are considered active and effective regimens at the time of disease relapse [26].

Carfilzomib is a next-generation PI that first received approval in 2013 for the treatment of RRMM. Carfilzomib-containing regimens play a crucial role in the relapsed setting and can be effective even in patients with resistance to bortezomib-based therapy [26].

The IRD combination (ixazomib, lenalidomide, dexamethasone) demonstrated superior efficacy compared to RD (lenalidomide-dexamethasone) and was approved in 2015 for use in patients who have received at least one prior line of therapy [26, 27].

As lenalidomide is a backbone of both combination and maintenance therapy, pomalidomide has become the subsequent immunomodulatory drug (IMiD) of choice for RRMM. Results from the phase 3 OPTIMISMM trial confirmed the superiority of the PVD regimen (pomalidomide, bortezomib, dexamethasone) compared to VD (bortezomib, dexamethasone) in patients with RRMM. A subgroup analysis focusing on first relapse demonstrated its efficacy, particularly in cases where prior lenalidomide treatment had failed [6, 26, 28].

Daratumumab is a widely utilized agent for the treatment of RRMM [26, 28]. The POLLUX trial demonstrated that its addition to a lenalidomide-dexamethasone backbone significantly improves PFS. The CASTOR trial confirmed that the DVD combination (daratumumab, bortezomib, dexamethasone) also prolongs PFS [28]. Furthermore, results from the CANDOR study showed a significant increase in PFS for patients receiving the DKD regimen (daratumumab, carfilzomib, dexamethasone) compared to those receiving carfilzomib and dexamethasone alone [5, 28]. Consequently, the following regimens are approved: DRD, DVD, DPD (daratumumab, pomalidomide, dexamethasone), and DKD [26].

A randomized trial confirmed the efficacy of the combination containing elotuzumab – a mAb targeting the signaling lymphocytic activation molecule family member 7. The EPD regimen (elotuzumab, pomalidomide, and dexamethasone)

proved to be more effective than therapy with PD (pomalidomide and dexamethasone) alone. Based on these results, EPD was approved for patients with MM who have received at least two prior lines of therapy, including lenalidomide and a PI [26].

The FDA initially approved isatuximab for the treatment of RRMM in patients who have received at least two prior lines of therapy, including lenalidomide and a PI. Isatuximab has demonstrated high efficacy in combination with carfilzomib and dexamethasone (Isa-Kd) [18, 22, 26].

Selinexor, a selective inhibitor of nuclear export, is an innovative agent that received accelerated approval from the FDA in 2019 for use in combination with dexamethasone in patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two PIs, two IMiDs, and an anti-CD38 mAb [28]. In 2020, the FDA also approved the use of selinexor in combination with bortezomib and dexamethasone for patients with MM who have received at least one prior line of therapy [11, 26, 28].

Venetoclax is a selective BCL-2 inhibitor. According to the phase 3 BELLINI trial, the addition of venetoclax to bortezomib and dexamethasone demonstrated an improvement in the OS rate in patients with t(11;14) or high BCL2 expression; however, it led to an increased mortality rate compared to placebo. The drug is associated with increased mortality in RRMM [6, 16, 26, 28]. The NCCN guidelines have included venetoclax in combination with dexamethasone, with or without the addition of daratumumab or a PI, as treatment options for patients with the t(11;14) translocation [17].

CAR T-cell therapy is a novel treatment approach demonstrating promising efficacy in the management of RRMM [13, 23, 28]. It is a complex, multi-stage process consisting of patient selection, cell collection (leukapheresis), CAR T-cell manufacturing, lymphodepleting chemotherapy, cell infusion, and subsequent long-term monitoring [23].

Patient selection for CAR T-cell therapy is dependent on health status, prior lines of chemotherapy, risk factors, and social factors. Once eligibility is confirmed, leukapheresis is performed to collect mononuclear cells. The T-cells are genetically modified, expanded ex vivo, and cryopreserved until infusion. Prior to infusion, patients receive lymphodepleting chemotherapy to prepare the immune system. Following the cell infusion, the peak expansion in the body occurs within 1-2 weeks, necessitating intensive medical supervision during this period [23].

The widespread adoption of CAR T-cell therapy is limited due to the requirement for specialized facilities to manage potential adverse effects, such as cytokine release syndrome and neurotoxicity [13, 24, 28, 30].

According to contemporary research data, the following treatment regimens are recommended for

patients with MM who have experienced disease relapse after four prior lines of therapy. The FDA has currently approved three bispecific antibodies (elranatamab-bcmm, talquetamab-tgvs, and teclistamab-cqyv) and two CAR T-cell therapies (idecabtagene vicleucel and ciltacabtagene autoleucel), which are included in the NCCN guidelines as preferred options for the treatment of RRMM following at least four prior lines of therapy, including an anti-CD38 mAb, a PI, and an IMiD [13, 17].

Despite the availability of numerous therapeutic options, the majority of patients will eventually develop refractoriness to all major drug classes. Additional therapeutic approaches include anthracycline-based regimens such as PAD or VDT-PACE, regimens utilizing selinexor, as well as bendamustine-based protocols, specifically bendamustine in combination with lenalidomide and dexamethasone or with bortezomib and dexamethasone. For younger, high-risk patients with an available donor, allogeneic transplantation is also considered a potential treatment option [17, 26].

Contemporary Approaches to Supportive Care in MM Management. The management of bone disease remains a significant unmet need in MM. Diffuse osteopenia and/or osteolytic bone lesions are observed in approximately 85% of MM patients [12, 17]. These complications cause pain syndromes, pathological fractures, and spinal cord compression, which can lead to disability and a significant decline in quality of life. Research by Derenson et al. demonstrated that monthly intravenous infusions of pamidronate reduce pain, improve functional capacity, and delay skeletal-related events. Zoledronic acid provides equivalent benefits; however, data from the Zervas et al. study indicate it carries a 9.5-fold increased risk of osteonecrosis of the jaw compared to pamidronate [17].

NCCN guidelines recommend the use of either bisphosphonates or denosumab for all patients undergoing treatment for symptomatic MM, irrespective of the presence of confirmed bone lesions. NCCN experts prefer denosumab for patients with impaired renal function [12, 17]. Patients receiving bisphosphonates require monitoring of renal function and should undergo a dental examination before and during therapy [17]. There is a clear need for novel drug classes that target bone remodeling pathways [24].

An essential aspect of successful chemotherapy administration in MM patients is the timely prophylaxis of infectious complications. The relevance of this issue remains extremely high, as MM patients are at increased susceptibility to infections due to immunosuppression caused by the disease itself and chemotherapy, advanced age, and the presence of comorbidities. In 2022, the IMWG (International Myeloma Working Group) published guidelines for the prevention and management of

infections in MM patients. Prophylactic use of levofloxacin during the initial 2-3 months of primary therapy is recommended to reduce the risk of infection development. Patients receiving long-term steroid therapy or anti-CD38 mAb treatment should be considered for prolonged prophylaxis with trimethoprim-sulfamethoxazole against *Pneumocystis jirovecii* pneumonia. Acyclovir or valacyclovir should be prescribed for herpes zoster prophylaxis to those receiving PIs, anti-CD38 mAbs, or elotuzumab. For patients with hypogammaglobulinemia undergoing daratumumab treatment who suffer from frequent respiratory infections, intravenous immunoglobulin administration may be considered [16, 25]. Furthermore, myeloma patients exhibit a suboptimal response to COVID-19 vaccines; therefore, they should receive booster doses according to current guidelines, and post-vaccination antibody levels should be assessed [15, 29].

The prevention of chemotherapy-induced adverse effects, particularly hepatotoxicity, is a key objective in the comprehensive management of patients. Rational nutritional support plays a vital role in improving treatment outcomes and maintaining the body's capacity to withstand the therapeutic burden.

Involving specialist dietitians and conducting nutritional consultations helps to correct nutrient deficiencies and assists in adapting to chemotherapy-induced appetite changes [9].

Timely and effective prophylaxis against the development of hepatotoxic reactions during chemotherapy in MM patients allows for a reduction in the risk of toxic complications and, consequently, enhances treatment efficacy. Contemporary research confirms that the application of L-ornithine-L-aspartate is one of the most effective agents for the prevention of hepatotoxic and nephrotoxic injury in MM patients undergoing chemotherapy [20].

Despite significant therapeutic progress over the last two decades, MM remains an incurable oncohematological disease that leads to reduced life expectancy [3, 9, 18, 19, 23]. A crucial aspect is ensuring patient access to innovative medicinal agents, which is often possible through participation in clinical trials. This is particularly important for patients with multiple prior lines of chemotherapy who have limited options for effective treatment. Participation in clinical trials not only opens new opportunities for them but also contributes to the refinement of future treatment modalities [24].

Conclusion

A fundamental principle in the management of MM patients is the initial determination of eligibility for ASCT. Performing ASCT increases the rate of clinico-hematological remission achievement and improves patient survival outcomes.

The development and implementation of novel therapeutic approaches remains a critical focus. Furthermore, enrolling patients in clinical trials is essential, particularly for those with RRMM and patients with high-risk disease features.

An ongoing area of significant importance is the investigation of supportive care strategies, particularly agents for bone remodeling. This is critically important for improving patient quality of life and reducing the risk of skeletal-related complications.

Prospects for further research include the development and evaluation of novel therapeutic approaches, optimization of treatment strategies for patients with MM, RRMM and high-risk disease, and improvement of supportive care that could reduce treatment-related toxicity and improve the quality of life.

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ORCID: Stadnik Y.O. <https://orcid.org/0009-0006-1598-3443>, Maslova G.S. <https://orcid.org/0000-0002-4729-1736>.

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