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Review Article

Innovative treatments for multiple myeloma in adults who are not candidates for stem transplantation

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ABSTRACT

In the reviewed article, we evaluated the different innovative therapeutic options for the treatment of multiple myeloma in patients who are not candidates for stem cell transplantation. Multiple myeloma (MM) is a malignant neoplasm whose incidence is increasing in developed countries. It represents around 1% of neoplastic diseases and 13% of hematologic cancers. It arises from an asymptomatic proliferation of premalignant monoclonal plasma cells derived from B cells after they pass through the germinal center stage in various genetic steps and microenvironmental changes. Although in this study we discuss various therapeutic options that seem promising, we must keep in mind that these still require further research for their application in order to reduce the adverse effects that some of them may present.

Keywords: Multiple myeloma, Treatment, Diagnosis, Innovation, Survival

INTRODUCTION

Multiple myeloma (MM) arises from an asymptomatic proliferation of premalignant monoclonal plasma cells, which originate from B cells after they pass through the germinal center phase in various genetic steps and microenvironmental changes. These changes can lead to the transformation of these cells into a malignant tumor.

It is often associated with rearrangements affecting the IgH locus and several proto-oncogenes. Among the loci commonly involved in translocations with the heavy chain gene of Ig on chromosome 14q32 are the cell cycle regulatory genes cyclin D1 on chromosome 11q13 and cyclin D3 on chromosome 6p21. Deletions of chromosome 17p also occur, affecting the tumor suppressor TP53 locus, which is associated with poor prognosis.[1] There are still some alterations for which the pathophysiology is not yet described, such as on chromosome 1q, present in 40% of new cases of myeloma, also associated with poor prognosis.[2]

MM is a malignant proliferation of plasma cells derived from a single clone. The tumor, its products, and the host response to them cause various organ dysfunctions and symptoms such as bone pain or fractures, renal insufficiency, increased infection susceptibility, anemia, hypercalcemia, and sometimes coagulation disorders, neurological symptoms, and vascular manifestations of hyperviscosity.[3]

MM is a malignant neoplasm with increasing incidence in developed countries. It represents about 1% of neoplastic diseases and 13% of hematological cancers. In Western countries, the annual age-adjusted incidence is 5.6 cases per 100,000 people.

It is approximately 1.5 times more common in men than in women worldwide.[4] The median age at diagnosis is close to 70 years, with 37% of patients under 65 years old, 26% between the ages of 65 and 74, and 37% aged 75 or older.[5] Additionally, 5-10% of cases occur in adults under 40 years old.[1] The risk of being diagnosed with MM from

birth to age 74 is 0.24% in men and 0.17% in women, making the disease approximately 1.5 times more likely in men.[4]

In 2018, it was estimated that 106,000 people worldwide died from MM, accounting for 1.1% of all cancer deaths. Approximately 59,000 were men, and 47,000 were women. Although incidence has increased over recent decades, mortality has declined due to the dramatic increase in survival. Survival rates are somewhat dependent on the stage at diagnosis, with a 5-year survival rate of 74.8% for those with localized disease (which represents only 5% of all cases) and 52.9% for systemic MM (the remaining 95% of diagnoses).[4]

This plasma cell neoplasm is one of the models of human neoplastic diseases since it arises from a single tumor stem cell. Furthermore, tumor cells produce a marker protein (myeloma immunoglobulin) that allows quantification of the total body tumor cell burden.

MM primarily affects the bone marrow and bones, causing what are known as "CRAB" symptoms: hypercalcemia (>10 mg/dl); renal impairment: creatinine >2 mg/dl or creatinine clearance <40 ml/min; anemia (Hb <10 g/dl or 2 g/dl below normal); and bone involvement: one or more osteolytic lesions. Just one of these criteria is enough to suspect MM, causing bone pain, lytic lesions, fractures, and increased susceptibility to infection. Other symptoms include nausea, vomiting, malaise, weakness, weight loss, peripheral neuropathy, hyperviscosity, and neutropenia. It is challenging to diagnose in its early stages, as there are no symptoms, so most multiple myeloma patients are symptomatic at the time of initial diagnosis and require treatment with cytotoxic chemotherapy. While bone disease is predominant, it can spread to lymph nodes and extramedullary sites.

The neoplastic plasma cells mediate bone destruction, the main pathological feature of MM. Particularly important is that myeloma-derived MIP1a protein stimulates the expression of the NF-kB ligand receptor activator (RANKL) by bone marrow stromal cells, which in turn activates osteoclasts.[6]

Diagnosis is based on the presence of at least 10% clonal plasma cells in the bone marrow and monoclonal protein in the serum or urine. In non-secreting myeloma patients, the diagnosis is based on the presence of 30% monoclonal plasma cells in the bone marrow or a biopsy that documents a plasmacytoma.

DEVELOPMENT

Survival has more than doubled in recent decades due to the introduction of new chemotherapy combinations, targeted small molecule inhibitors, and monoclonal antibodies. Initial treatment of symptomatic MM patients depends on the risk stratification of MM and the patient's eligibility for hematopoietic stem cell autotransplantation (HCT), considering any pre-existing comorbidities (e.g., neuropathy or renal insufficiency).[4]

Cereblon E3 ligase modulators

These drugs have pleiotropic antitumor and immunomodulatory activity by specifically binding to the cereblon protein, promoting the recruitment of protein substrates Ikaros and Aiolos, which triggers polyubiquitination and degradation of these substrates, resulting in depletion of c-MYC and interferon regulatory factor 4 (IRF4), both of which are necessary for myeloma cell growth and survival. Iberdomide has a 10 to 20 times greater affinity than other drugs for the cereblon protein gene, inducing more potent and efficient substrate degradation, which is associated with greater antimyeloma and immunostimulatory activity.

Currently, iberdomide is being tested in combination with proteasome inhibitors and monoclonal antibodies targeting CD38 to evaluate the optimal dose and safety in relapsed or refractory MM patients. Adverse events include anemia (15-52%), neutropenia (9-45%), thrombocytopenia (3-45%), infections (10-15%), and pneumonia (3%).

Mezingdomide is a new agent that showed *in vitro* activity, with initial published results indicating that the maximum tolerated dose has been 1.0 mg and that the overall response rate has been 21% for all evaluable patients, and 48% at the therapeutic dose of 1.0 mg. Adverse reactions (ARs) grade 3-4 due to treatment were reported in 88% of patients, with the most frequent being: neutropenia (53%), infections (30%), anemia (29%), thrombocytopenia (17%), and fatigue (9%).[1]

Humanized monoclonal antibodies

Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with direct antitumor and immunomodulatory activity. A study by Facon et al included 737 patients randomly assigned: 368 to the daratumumab group and 369 to the control group. The median age was 73 years (range 45 to 90), and 14.3% of the patients had a high-risk cytogenetic profile.[7]

The results showed that the risk of disease progression or death was 44% lower in the daratumumab group than in the control group. However, the benefit of daratumumab with respect to progression-free survival was not as high in the subgroup of patients with a high-risk cytogenetic profile compared to the subgroup of patients with a standard cytogenetic risk profile, where greater efficacy was observed.[7]

Patients in the daratumumab group received treatment for a longer period and received less lenalidomide than the control group, possibly due to a higher incidence of adverse events leading to dose interruption or modifications in this group. Nevertheless, the efficacy of

the daratumumab-based regimen was not affected by the lower dose of lenalidomide.[7]

The daratumumab group had a higher incidence of neutropenia and infections (including pneumonia) than the control group; however, the percentage of patients who discontinued treatment due to these adverse events was low. This study involved newly diagnosed multiple myeloma patients who were not eligible for stem cell transplantation. The evaluation showed that the addition of daratumumab to lenalidomide and dexamethasone resulted in significantly longer progression-free survival, a higher response rate, and a longer-lasting response than lenalidomide and dexamethasone alone.[7]

Combining therapies with different mechanisms of action has improved outcomes in relapsed or refractory multiple myeloma patients. For example, when discussing monoclonal antibodies, elotuzumab is a humanized immunoglobulin G1 (IgG1) that binds to signaling lymphocyte activation molecule family member 7 (SLAMF7), a glycoprotein highly expressed on the surface of myeloma cells, natural killer (NK) cells, and some immune cells but not on other normal cells or tissues. Its mechanism involves antibody-dependent cellular cytotoxicity mediated by NK cells.

On the other hand, pomalidomide is an immunomodulatory agent with structural and mechanistic properties similar to lenalidomide but can provoke distinct biological effects. Pomalidomide is approved in combination with dexamethasone for patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor, and whose disease is refractory to their last therapy. The combination of elotuzumab and pomalidomide may have synergistic clinical effects in patients who have relapsed after lenalidomide treatment or are refractory to lenalidomide. Pomalidomide may enhance the destruction of myeloma cells mediated by immune cells through elotuzumab, with a favorable safety profile.[8]

To evaluate this treatment, we relied primarily on a study conducted by Meletios et al, where the investigated patients had received two or more prior lines of therapy, including at least two consecutive cycles of lenalidomide and a proteasome inhibitor, either alone or in combination. In this study, all patients had multiple myeloma that was refractory to their last therapy. The patients were randomly assigned in a 1:1 ratio to receive elotuzumab plus pomalidomide and dexamethasone (elotuzumab group) or pomalidomide and dexamethasone (control group). A total of 60 patients were assigned to the elotuzumab group, and 57 were assigned to the control group.[8]

The results showed that the addition of the monoclonal antibody elotuzumab to pomalidomide and dexamethasone resulted in a significant improvement over pomalidomide and dexamethasone alone in treating relapsed or refractory multiple myeloma. The overall response rate in the elotuzumab group was twice as high as in the control group. Therefore, these data suggest that elotuzumab plus pomalidomide and dexamethasone is an effective combination with a good safety profile, but it still needs further evaluation with more studies to confirm its efficacy.[8]

Bispecific antibodies

These antibodies exert their action by binding to and neutralizing extracellular molecules on the tumor cell. They form strong bonds with specific antigens, blocking intracellular signaling pathways by preventing protein-protein interactions. Few neoplasms are entirely dependent on a single signaling pathway, so bispecific antibodies are rarely curative in cancer. These antibodies were designed to bind a tumor cell and a cytotoxic effector cell (NK cells or T lymphocytes) within the same antibody.

Target molecules include B-cell maturation antigen (BCMA) or CD269, a tumor necrosis factor involved in B-cell proliferation, maturation, survival, and differentiation. Another target is CD38, a surface glycoprotein found in plasma cells and, to a lesser extent, in myeloid, lymphoid, NK cells, red blood cells, and platelets.

Additionally, it is expressed in non-hematopoietic tissues, which may result in many adverse effects and poses a challenge for development. GPRC5D, a receptor whose function is unknown, is highly expressed in bone marrow plasma cells and keratinized structures but not in other healthy cells. Lastly, the Fc receptor homolog 5 is expressed exclusively in B-lineage cells and overexpressed in MM cells.[5]

Some compounds undergoing phase 2 studies include the following.

Teclistamab

An anti-CD3/anti-BCMA antibody that binds CD3+ T cells with BCMA+ plasma cells, activating T cells followed by cell death and lysis. It was the first bispecific antibody approved by the FDA in October 2022, and changes in BCMA levels were related to the response. Common adverse effects are hematological (60%), followed by infections and cytokine release syndrome.

Elranatamab

A bispecific antibody targeting BCMA and CD3, activating and directing cytotoxic T cells against tumor plasma cells. All patients reported adverse events. The most common hematological toxicity was neutropenia, followed by anemia.

Liveseltamab

It includes targets BCMA and CD3.

Talquetamab

A first-in-class IgG4 bispecific antibody targeting GPRC5D/CD3.[5]

CAR-T cells

This therapy is performed by collecting T cells through the extraction of white blood cells (including T cells) from the patient's blood via leukapheresis. Two intravenous lines are used: blood is drawn through one line to separate white blood cells, and the blood is returned to the body via the other line. Once the white blood cells are extracted, the T cells are separated, sent to the laboratory, and genetically modified to express a chimeric antigen receptor (CAR) designed to recognize a specific antigen on the patient's cancer cells. In this way, the T cells become CAR-T cells, which are produced, multiplied, and infused into the patient.

In some cases, prior chemotherapy is required before the therapy to improve the performance of CAR-T cells. Numerous trials are currently underway, including CAR-T cells targeting CD19 and/or B-cell maturation antigen (BCMA). BCMA is expressed on myeloma cells and is restricted to plasma cells and some mature B cells. The first CAR-T therapy developed for MM targeted this surface protein. CAR-T cells targeting BCMA have shown very promising results in phase I clinical trials for patients with relapsed or refractory multiple myeloma, increasing survival.

There are other CAR-T options, such as the following.

CS1/SLAMF7

A molecule expressed in immune cells (NK, T, B cells, dendritic cells), with activating or suppressive functions depending on the cell type. Preclinical trials have shown that anti-CS1/SLAMF7 CAR-T cells exhibit *in vitro* and *in vivo* cytotoxicity in myeloma models. Some of the most severe adverse effects include cytokine release syndrome, with the most common being anemia, fever, decreased white blood cell counts, hypophosphatemia, and hypertension.

GPRC5D

A G-protein coupled receptor expressed in MM that has demonstrated anti-myeloma activity in *in vivo* models.

CD44

It has garnered significant interest for immunotherapy due to its high heterogeneity resulting from post-transcriptional modifications, including glycosylation patterns. These may show differential behavior in tumors. Recently, it was confirmed that a second-generation CAR (CD28) targeting CD44v6 has antitumor efficacy in MM models. This led to the development of a clinical trial (NCT04097301) based on CD44v6 CAR therapy in patients with relapsed/refractory multiple myeloma (RRMM) as part of the European H2020 research program. The study started in 2018, and some results are known, such as adverse events (AEs), with severe cases including pneumonia and the most frequent being neutropenia, anemia, and fever. More results are awaited to continue the study of this therapy.[1]

Proteasome inhibitors

The incorporation of proteasome inhibitors and immunomodulatory drugs into the standard of care has improved outcomes for multiple myeloma patients over the past 10 years, although most patients eventually relapse. Treatment with daratumumab has demonstrated substantial efficacy as a single agent and a manageable safety profile in phase 1-2 studies for treatment-resistant or relapsed multiple myeloma, with overall response rates of 29% and 36%.[9]

A study by Dimopoulos et al on daratumumab, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma showed that this combination provides therapeutic benefits without dose-limiting toxicities and an overall response rate of 81%, including a strict complete response rate of 25%. At 18 months, the progression-free survival rate was 72%, and the overall survival rate was 90%.[9]

Adverse events occurred in 10% or more of the patients in the daratumumab group versus the control group, including neutropenia, diarrhea, upper respiratory tract infections, and cough, most of which resulted from longer exposure to treatment in the daratumumab group. Regarding non-hematological adverse events, the incidence of grade 3 or 4 diarrhea, fatigue, nausea, and dyspnea was slightly higher in the daratumumab group compared to the control group. Results showed that the addition of daratumumab to lenalidomide and dexamethasone significantly prolonged progression-free survival and was associated with a 63% lower risk of disease progression or death than lenalidomide and dexamethasone alone among patients with multiple myeloma who had received one or more prior lines of therapy. Daratumumab combined with lenalidomide and dexamethasone was associated with clinically manageable adverse events consistent with the known toxic effects of lenalidomide, dexamethasone, and daratumumab. Despite the higher rates of neutropenia in the daratumumab group, the rate of grade 3 or 4 infections was only slightly higher in the daratumumab group than in the control group (28% versus 23%). Treatment discontinuation rates due to adverse events were low and similar between the two groups.[9]

MM has a better survival outcome than other hematological neoplasms, such as aggressive lymphoma and acute leukemia. Survival rates have improved as many new drugs have been developed. Conventional therapies,

such as proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), as well as monoclonal antibodies, checkpoint inhibitors, and chimeric antigen receptors, have shown promising results. In a study by Cho S et al., 59 patients newly diagnosed with MM and treated with bortezomib, melphalan, and prednisolone (VMP) were enrolled. All patients were ineligible for transplantation. The median patient age was 72 years, with a male-to-female ratio of 1:1.[10]

Treatment with the combination of the alkylating agent melphalan and prednisolone (MP protocol) has been a standard regimen for nearly 30 years. About 40% of patients respond to the MP combination, with an average remission duration of 2-2.5 years. Oral melphalan and prednisolone treatment can reduce the plasma cell burden but rarely results in complete hematological remission, significant organ responses, or improved survival, and it is no longer used. Replacing prednisolone with dexamethasone produces higher response rates and more durable remissions, although dexamethasone is not always well-tolerated in patients with significant edema or heart disease.[3]

Response evaluation was conducted after each treatment cycle using serum/urine protein electrophoresis (PEP) and serum free light chain analysis. All patients were treated with VMP according to the VISTA trial schedule, with subcutaneous bortezomib injections, receiving a total of 9 cycles. Disease progression was the primary reason for treatment discontinuation, followed by death, and one patient refused to continue treatment.[10]

During VMP treatment, 84.7% of patients experienced dose reductions, and 23.7% of patients had their doses reduced twice. One-third of patients (32%) experienced dose reductions in the first cycle, with 14 patients (28%) and 15 patients (30%) having dose reductions in the second and third cycles, respectively. There was a high rate of dose reduction in the first cycle, showing a trend towards reducing doses early on. When patients complained of adverse effects, physicians always discussed dose reductions with them. Almost all dose reductions (90%) were performed before the third cycle, so the proportion of dose reductions significantly decreased by the fourth cycle.

The primary reason for dose reduction was non-hematological toxicity (92.7%), including peripheral neuropathy (36.6%). Other non-hematological toxicities included weakness, vomiting, skin rash, infection, dizziness, diarrhea, mucositis, and disorientation. Dose reduction makes treatment easier to continue, eventually providing the opportunity to administer more drugs and achieve a better response.

The most widely approved regimens for elderly patients are lenalidomide plus dexamethasone, and outside the United States, melphalan-prednisone-thalidomide or melphalan-prednisone-bortezomib. In patients with at least one prior line of therapy, daratumumab combined with standard regimens (bortezomib-dexamethasone and lenalidomide-dexamethasone) significantly prolonged progression-free survival and induced higher response rates. Daratumumab-based combinations reduced the risk of disease progression or death by more than 60%.[11]

In the study by Mateos et al, patients with documented, newly diagnosed multiple myeloma who were ineligible for high-dose chemotherapy with stem cell transplantation due to coexisting conditions or age (65 years or older) were included. Patients were randomly assigned in a 1:1 ratio to receive daratumumab combined with bortezomib, melphalan, and prednisone (daratumumab group) or bortezomib, melphalan, and prednisone alone (control group).[11]

All patients received up to nine cycles (42 days) of subcutaneous bortezomib, oral melphalan, and oral prednisone. In the experimental group, daratumumab was administered intravenously at a dose of 16 mg per kilogram of body weight, with oral or intravenous dexamethasone at a dose of 20 mg once per week in cycle 1, every 3 weeks in cycles 2 to 9, and every 4 weeks thereafter. Dexamethasone at a dose of 20 mg was substituted for prednisone on day 1 of each cycle.[11]

Of 706 patients, 350 were assigned to the daratumumab group, and 356 to the control group. The median age at the start of the study was 71 years, and the median time since diagnosis was 0.8 months. The median treatment duration was 14.7 months in the daratumumab group and 12.0 months in the control group.

The primary efficacy endpoint was progression-free survival. The secondary safety endpoint was evaluated using adverse event reports. The most common adverse events of any grade were neutropenia, thrombocytopenia, peripheral sensory neuropathy, anemia, upper respiratory tract infection, diarrhea, fever, and nausea. The addition of daratumumab to bortezomib, melphalan, and prednisone did not increase overall toxicity. Except for infections, adverse events were balanced between the daratumumab and control groups, with a lower rate of peripheral sensory neuropathy in the daratumumab group.[11]

The trial by Mateos et al demonstrated that daratumumab combined with bortezomib, melphalan, and prednisone produced significant clinical benefits compared to bortezomib, melphalan, and prednisone alone in newly diagnosed multiple myeloma patients who were ineligible for stem cell transplantation. Overall, daratumumab in combination with this standard care regimen was associated with infusion-related reactions and more infections, including a higher rate of pneumonia (which did not result in higher rates of discontinuation or death); the usual toxic effects related to chemotherapy did not increase with the addition of daratumumab.[11]

To evaluate the reduced frequency therapeutic regimen of bortezomib and dexamethasone for elderly patients with relapsed and/or refractory multiple myeloma, we relied on a study by Ozaki et al, which discusses bortezomib. It is one of the most widely used novel drugs for treating MM. However, twice-weekly intravenous administration is associated with undeniable adverse events and treatment discontinuation. Therefore, the long-term efficacy and feasibility of reduced-frequency intravenous bortezomib treatment were evaluated in elderly patients with relapsed and/or refractory MM. A total of 47 patients without prior bortezomib treatment (median age 75 years) received bortezomib (1.3 mg/m^2 intravenously) and dexamethasone (20 mg intravenously or orally) on days 1, 8, and 15 of each 4-week cycle for 8 cycles. Patients who achieved stable disease or improvement after 8 cycles were followed up without treatment until disease progression. Subsequent therapy was determined by the respective attending physician. Twenty-six patients completed the 8 planned cycles. The best responses were strict complete response in 5 patients, very good partial response in 3, partial response in 15, stable disease in 18, and disease progression in 6. The median progression-free survival and overall survival were 9.6 and 35.1 months, respectively. After progression, 11 patients were withdrawn using bortezomib-based regimens, and another 24 patients with immunomodulatory drugs. In terms of efficacy, this reduced-frequency bortezomib-dexamethasone regimen was comparable to previous trials. Regarding safety, the incidence and patterns of adverse events, such as diarrhea, constipation, and peripheral neuropathy, were consistent with the earlier study, but the incidence of severe peripheral neuropathy was much lower, observed in only 2% of cases. Therefore, our results suggest that this reduced-frequency intravenous bortezomib-dexamethasone regimen is an effective and safe therapeutic strategy for elderly patients with relapsed and/or refractory MM.

The multivariate analysis revealed that ISS 3, t (4; 14), and <4 cycles of therapy were significantly poor prognostic factors, and subsequent therapy with bortezomib-based regimens was a favorable factor for prolonged OS. Based on the results of this study, we can conclude that reduced-frequency treatment with bortezomib along with intravenous dexamethasone is an effective option for elderly patients with MM.[12]

Recently, treatment options for patients with relapsed and/or refractory multiple myeloma (RRMM) have expanded to agents that provide a new mechanism of action: antibody-based immunotherapy. The potential targets of monoclonal antibodies (mAbs) in MM are diverse and may include surface proteins of tumor cells involved in signaling, tumor growth, and survival, or cellular and non-cellular components of natural killer (NK) cells, or the bone marrow microenvironment. By targeting antigens present on tumor cells, mAbs activate the immune system against MM through direct cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity, or antibody-dependent cellular phagocytosis. Elotuzumab is a fully humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to human SLAMF7 (also CS1, CRACC). The unique epitope of elotuzumab is located within the proximal C2 domain of the SLAMF7 membrane. The exact role of SLAMF7 in myeloma cells is still unknown. Stable knockdown of SLAMF7 in MM cells resulted in decreased cell growth and colony formation in vitro, as well as reduced tumor burden and increased animal survival in a mouse xenograft model. Myeloma cell targeting to the bone marrow, adhesion, and survival within the bone marrow microenvironment were affected, indicating SLAMF7's involvement in MM pathogenesis. Elotuzumab induced significant ADCC against various MM cell lines and patient-derived MM cells in dose-dependent and SLAMF7-specific ways, regardless of these MM cells' sensitivity or resistance to conventional therapy. Elotuzumab could not directly induce cell death signals in MM cells. To mediate elotuzumab's antitumor activity towards myeloma cells, the presence of functional NK cells was required. The antitumor activity of elotuzumab has also been studied in combination with established therapies.[13]

According to the International Myeloma Working Group, the treatment of relapsed MM requires a systematic approach based on various patient-specific characteristics, including prior treatment, the degree and depth of response, treatment-related toxicities, and genetic risk stratification. Additionally, the selection of MM therapies demands careful consideration of the balance between maximizing efficacy and ensuring acceptable tolerability. Elotuzumab is the first mAb introduced in the treatment of MM that acts through a dual immuno-oncological mechanism. The addition of elotuzumab to lenalidomide and dexamethasone not only led to a significant improvement in PFS but also resulted in a promising course of the PFS curve, suggesting the potential for long-term immunological control of MM in a subset of patients. Additional clinical data on biomarkers, treatment of earlier stages of the disease, and studies on selected combination regimens are ongoing to further optimize the use of elotuzumab in patients with MM.[13,14]

Several studies have demonstrated that the bone marrow microenvironment (BMM) promotes the growth, survival, and drug resistance of MM cells through bidirectional interactions between MM cells and bone marrow stromal cells or the extracellular matrix. Although long-term outcomes in MM treatment have improved, intrinsic or acquired drug resistance necessitates the development of new therapeutic strategies. The study of molecules that regulate the crosstalk between MM cells and the BMM provides a foundation for identifying new potential targets to inhibit MM development. There is substantial evidence regarding the MM microRNA (miRNA) signature, which includes miRNAs that may be associated with myeloma pathogenesis, suggesting therapeutic potential in

antagonizing the growth of transformed plasma cells. miRNAs are a large class of evolutionarily conserved non-coding RNAs, typically 18 to 22 nucleotides in length, that act as post-transcriptional repressors of target genes by binding in an antisense manner to their untranslated regions. Several studies have reported that modulating miRNA levels in MM cells impairs their functional interaction with the bone marrow microenvironment and produces significant antitumor activity, even capable of overcoming the protective bone marrow milieu. In this context, the forced expression of tumor-suppressing microRNAs, such as miR-29, has been explored.[13]

In this study, we focused on the molecular mechanisms of tumor suppression mediated by miR-34a in the RPMI 8226 MM cell line and its role in modulating the response to cancer drugs, particularly γSI, sirtinol, and ZOL. The results showed that miR-34a exerts potent inhibition of cell viability by inactivating two key molecules involved in regulating cell proliferation and survival, AKT and ERK1/2, and induces apoptotic cell death by activating the extrinsic pathway. Several studies have demonstrated that inhibiting multiple components of the same signaling pathway is more effective compared to targeting individual components, as it mediates a more complete inhibition of signaling. Moreover, miR-34a has been shown to sensitize different types of cells to conventional drug treatments. Our data demonstrate that the forced expression of miR-34a in RPMI 8226 cells significantly enhances the antitumor effect of the three agents γSI, sirtinol, and ZOL. All these agents have proven efficacy in inducing growth inhibition across a wide range of experimental models, including MM cells.[13]

Pharmacological combinations

Patients who are not candidates for stem cell transplantation have a range of therapeutic pharmacological options; among the most common, as mentioned in the article published by Cao et al, is the use of lenalidomide + dexamethasone. A systematic review was conducted on studies published between 01 January 1988, and 26 April 2018, using servers such as PubMed, Embase, and The Cochrane Library. Additionally, conference proceedings from January 2015 to December 2018 were included, from the following: American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, European Society for Medical Oncology, and the International Myeloma Working Group.[15]

A total of 19,871 articles were obtained through the bibliographic search. The results of the present article suggest that daratumumab + bortezomib, melphalan, and prednisone (RVd) is the best pharmacological option compared to lenalidomide and dexamethasone + daratumumab (Rd) in newly diagnosed multiple myeloma patients who are not candidates for stem cell transplantation.[15]

New therapeutic regimen proposals have been considered for patients who are not candidates for stem cell transplants, including "RVD," which consists of lenalidomide, bortezomib, and dexamethasone. This regimen has shown fewer adverse effects when administered differently than the standard approach in elderly patients. The standardized dose of dexamethasone is 40 mg once a week; however, in elderly patients, reducing the dose to 20 mg resulted in fewer toxicological effects. Bortezomib, the drug most commonly associated with peripheral neuropathy, was modified from the standard intravenous dose of twice a week to a subcutaneous dose of once a week, leading to a considerable reduction in this adverse effect in elderly patients. An anti-CD38 antibody was included in some cases, which resulted in a deeper response, with a slight, almost imperceptible improvement.[2]

According to the results of the SWOG S0777 trial, the triple regimen VRd (i.e., bortezomib, lenalidomide, dexamethasone) improved response rates, response depth, progression-free survival, and overall survival compared to the previously approved first-line Rd regimen (lenalidomide, dexamethasone), making a three-drug regimen the mainstay of initial treatment for most MM patients.[4]

In patients who are not candidates for hematopoietic stem cell transplantation, two main regimens are used: RVD and Dara-RVD (which adds an anti-CD38 antibody). If lenalidomide is not available, melphalan can be used, or alternatively, cyclophosphamide can be included. The latter shows better 2-year survival rates and reduces the number of adverse effects, as it is an alkylating agent.[2]

Risk of adverse events in different multiple myeloma therapies

Chen et al examined the risk of adverse events associated with first-line treatment for myeloma. This study aimed to assess the risks of adverse events associated with multiple myeloma therapies in a large population-based cohort of elderly patients with MM. The study compared safety outcomes between novel agents: proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs), and other therapies; as well as between PI or IMiD-based regimens and combination regimens of PI plus IMiD. Among 2,587 patients with advanced MM, 2,048 (79%) received novel agents, and 539 (21%) received other therapies. Patients with preexisting anemia and thrombocytopenia were significantly more likely to receive novel agents (85.9% versus 82.4%, p=0.038; 13.8% versus 10.4%, p=0.036), while those with preexisting cardiovascular disease and hypertension were significantly less likely to receive novel agents (73.4% versus 79.8%, p=0.003; 81.3% versus 85.2%, p=0.035). The hazard ratios for anemia, peripheral neuropathy, and thromboembolic events for patients receiving novel agents compared to those receiving other therapies were 1.19, 1.57, and 1.31, respectively. The hazard ratios for anemia, neutropenia, and

thromboembolic events for patients receiving combination therapies with PI plus IMiD compared to those receiving PI or IMiD-based therapies were 1.31, 1.66, and 1.37, respectively. Novel agents significantly increased the risk of anemia, peripheral neuropathy, and thromboembolic events. Combination therapies of PI plus IMiD were associated with a significantly higher risk of anemia, neutropenia, and thromboembolic events.[17]

DISCUSSION

There are multiple treatment regimen options for MM, and patient survival largely depends on the appropriate management of each regimen. Therefore, it is imperative to maintain proper control over the medications to be administered in order to identify potential adverse effects that the patient may experience. If necessary, medication doses should be adjusted to minimize adverse effects, thus preventing patients from discontinuing treatment due to discomfort caused by the medications.

When discussing monoclonal antibodies, we see a very good response from patients when these drugs are added. The addition of daratumumab to lenalidomide and dexamethasone resulted in significantly longer progression-free survival, a higher and more durable response compared to lenalidomide and dexamethasone alone in patients who had not been previously treated for multiple myeloma. In the case of patients with relapsed or refractory multiple myeloma, the addition of the monoclonal antibody elotuzumab to pomalidomide and dexamethasone resulted in significant improvement over pomalidomide and dexamethasone alone, making this a viable therapeutic option in both cases. However, it is important to assess the best, specific, and individualized treatment for each patient, and ongoing studies are needed to further improve response expectations.

First-line treatment for MM generally includes PI and/or IMiD, which have improved patient survival. However, there remains an unmet need for medications that can achieve deep and sustained myeloma responses, especially during disease relapse. In particular, drugs with novel modes of action that exhibit additive or synergistic effects with established backbone regimens are needed. In recent years, compelling evidence has shown that miR-34a acts as a tumor suppressor in multiple cancer types by controlling the expression of several target proteins involved in cell cycle regulation, differentiation, and apoptosis. MRX34, a liposome-based miR-34a mimic, is the first miRNA mimic to enter clinical development and was already evaluated in a phase 1 clinical trial in cancer patients. We recently demonstrated that forced expression of miR-34a in MM cells induces the modulation of several pathways, such as ERK- and Akt-dependent signaling, which are specifically relevant in the pathobiology of MM.[13,18]

Our results suggest that reduced frequency of intravenous bortezomib + dexamethasone would undoubtedly be an effective and safe therapeutic strategy for elderly patients with relapsed or refractory multiple myeloma.[18]

It is well known that one of the therapeutic options for multiple myeloma patients is stem cell transplantation. A study was conducted to evaluate the quality of life of patients who were candidates for this surgical procedure. It was found that these patients were susceptible to a slow recovery process, cognitive decline, depression, and a higher risk of high-dose drug toxicity. However, benefits were observed through physical activity and maintaining an active cognitive state with memory and reasoning exercises, which significantly improved the prognosis.

Refractory disease can occur within 60 days after the last dose, so treatment must be individualized, depending on the aggressiveness or recurrence of symptoms. As a first-line treatment, lenalidomide is used, but if the patient develops resistance to it, other medications, such as proteasome inhibitors combined with daratumumab, can be employed. Immunomodulators like pomalidomide can also be used in such cases.

Therapy for MM has changed significantly over the past two decades. The emergence of drugs with novel mechanisms of action, their combinations, and the decreasing use of cytotoxic agents have become the standard treatment, leading to better outcomes for these patients. Proteasome inhibitors (PIs) such as bortezomib, carfilzomib, and ixazomib reduce clonal plasma cell expansion by blocking the nuclear factor kappa B (NF-kB) pathway, inducing apoptosis. Immunomodulators (IMiDs) like thalidomide, lenalidomide, and pomalidomide reduce the production of interleukin 6 (IL-6) and inhibit the NF-kB pathway through the CEREBLON complex while activating pro-apoptotic caspases. In recent years, the arrival of antibodies targeting transmembrane glycoproteins (anti-CD38), such as daratumumab (humanized) and isatuximab (chimeric), have shown direct apoptotic activity, complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cell phagocytosis as their main mechanisms of action in MM.[19]

Each additional line of treatment is associated with lower response rates, shorter duration of response, shorter treatment-free intervals, higher toxicity rates, and increased comorbidities, with response rates dropping to below 5% in patients who have undergone at least five lines of treatment. This can be attributed to treatment discontinuation, deterioration of functional status, and lack of response to previous therapies for MM.[20]

CONCLUSION

Despite discussing various promising therapeutic options in this study, it is important to note that these treatments still require further research for their application and to reduce the adverse effects that some of them present.

Overall, we found that the use of immunomodulators, proteasome inhibitors, and monoclonal antibodies form the basis of innovative treatments for multiple myeloma, particularly in patients who are not candidates for stem cell transplantation.

Regarding proteasome inhibitors, it was found that, in terms of safety, the incidence and patterns of adverse events such as diarrhea, constipation, and peripheral neuropathy were consistent, although the occurrence of severe peripheral neuropathy was much lower.

Elotuzumab is the first monoclonal antibody (mAb) introduced in the treatment of multiple myeloma that acts through a dual immuno-oncological mechanism. The addition of elotuzumab to lenalidomide and dexamethasone not only led to a significant improvement in progression-free survival but also resulted in a promising progression-free survival curve, suggesting the potential for long-term immunological control of multiple myeloma in a subset of patients. Additional clinical data on biomarkers, early-stage disease treatment, and studies on selected combination regimens are underway to further optimize the use of elotuzumab in multiple myeloma patients.

The data provide novel insights into miR-34a as a potential therapeutic agent against cancer in MM, enhancing the antitumor activity of cancer drugs. However, one of the main challenges remains the emergence of side effects associated with inhibitors, especially gastrointestinal tract cytotoxicity.

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