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Recent Advances in Multiple myeloma

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Multiple myeloma (MM) represents a malignant proliferation of plasma cells originating from a single clone. The tumour causes bone pain, fracture, anaemia, and other infections. Patients present with MM are symptomatic and need cytotoxic chemotherapy. Previously, melphalan and glucocorticoid were accepted as first-line treatments. Recently, immunomodulatory drugs and proteasome inhibitors have become the treatment of choice. There are several new drugs approved for multiple myeloma: monoclonal antibodies, nuclear export inhibitors, B-cell maturation antigen (BCMA)-directed antibody, CAR T-cell therapy, histone-deacetylase inhibitor, and stem cell mobilizer. Drugs like cobemetinib are being evaluated for potential role in the treatment of MM. Pharmacogenomics and precision medicine also play a crucial role in the treatment of multiple myeloma.

Keywords: B-Cell Maturation Antigen (BCMA)-Directed Antibody; CAR-T Cell Therapy; Immunomodulator Analogues (Imid); Multiple Myeloma(MM); Momoclonal Antibodies (Mab).

Multiple myeloma (MM) represents a malignant proliferation of plasma cells originating from a single clone. The tumour results in neurologic symptoms, bone pain or fracture, renal failure, higher susceptibility to infections like pneumonia and pyelonephritis, normocytic and normochromic anaemia, hypercalcemia, and possibly clotting abnormalities, as well as signs of hyperviscosity.[1,2,3] The median age at diagnosis is 70 years.[4,5,6] Men are more impacted than women,[7,8,9] and blacks have nearly twice the incidence than whites.[10]

The most recent numbers from the Global Cancer Observatory (GLOBOCAN) suggested that there were 1,76,404 instances of MM worldwide in 2020, making up 1.2% of all cancer diagnoses.[11]

Treatment modalities

Individuals who initially present with multiple myeloma are symptomatic and need cytotoxic chemotherapy. Melphalan (an alkylating agent) and prednisone (a glucocorticoid), together known as the "MP protocol," was long accepted as the conventional first-line therapy.[12,13] Proteosome inhibitors and immunomodulatory analogues (IMiDS) have recently become important first-line treatments.[14,15,16] Currently, the most active treatment is a triplet regime consisting of a proteosome inhibitor, an IMiD and dexamethasone or a doublet regimen consisting of a proteasome inhibitor and dexamethasone.[17,18]

Currently prescribed drugs for multiple myeloma

i. Alkylating agents- melphalan and cyclophosphamide

ii. Anthracyclines- cyclophosphamide and doxorubicin

iii. Corticosteroid- dexamethasone

iv. Immunomodulatory drug (IMiD)- Thalidomide,

lenalidomide and pomalidomide
v. Proteasome inhibitor- Bortezomib, carfilzomib and ixazomib
vi. MonoclonalAntibodies- Daratumumab, Elotuzumab and Isatuximab
vii. Nuclear export inhibitor- Selinexor
viii. B-cell maturation antigen (BCMA)-directed antibody- Belantamab mafodotin
ix. CAR T-cell therapy-Idecabtagene vicleucel, Ciltracabtagene autoleucel
x. Histone- deacetylase inhibitor - Panobinostat
xi. Bisphosphonate- Pamidronate and zoledronate
xii. Stem cell mobilizer-Prelixafor

Thalidomide is a recognised treatment for refractory or relapsed forms of MM. The recommended dosage of thalidomide in combination with dexamethasone is 200 mg once daily (in a 28-day treatment cycle). The dose-limiting adverse effects of thalidomide are sedation, fatigue, constipation and sensory neuropathy. Drug withdrawal alleviates the neuropathic symptoms, however, long-standing sensory loss might not reverse. The drug should be used cautiously in patients with diabetes[19,20]. Thalidomide enhances the sedative effects of barbiturates and alcohol and the catatonic effects of chlorpromazine[21,22]. Renal failure necessitates no dose modification.

Lenalidomide is a IMiD analog of thalidomide. The standard dosage of lenalidomide is 25 mg/d for 21 days in a 28-day cycle. Lenalidomide results in bone marrow depression and leukopenia[23,24]. Hepatotoxicity and renal dysfunction are rare adverse effects. Lenalidomide can trigger a tumour flare-up and significant lymph node enlargement in some patients of chronic lymphocytic leukemia.

Pomalidomide is the newest IMiD analogue of thalidomide. It is used in conjunction with dexamethasone, for patients with MM who have had at least two prior treatments with lenalidomide and a proteasome inhibitor and have shown signs of disease progression within or after 60 days of completion of the last treatment. It is taken orally at a dose of 4 mg per day on day 1 through 21 of repeated 28-day cycles. The most frequently reported side effects (e"30%) were asthenia and fatigue, neutropenia, anaemia, constipation, nausea, diarrhoea, dyspnea, upper respiratory tract infections, back pain, and pyrexia. Pomalidomide has a black box warning for embryo-fetal toxicity and venous and arterial thromboembolism[25]. Pomalidomide is a substrate for several cytochrome P450 enzymes[26]. Studies revealed that co-administration of pomalidomide with fluvoxamine (CYP1A2 inhibitor) in the presence of ketoconazole (CYP3A4/5 inhibitor) almost doubled pomalidomide exposure[27]. Pomalidomide's ability to be used in thalidomide and lenalidomide resistant cases pose a potential benefit of this analogue[28,29].

Bortezomib is currently being used as initial therapy as well as for refractory and relapse cases of MM. It exerts its effects by inhibiting of the 26S proteosome. Bortezomib is administered at a dose of 1.3 mg/m^2 as an intravenous bolus on days 1, 4, 8, and 11 of each 21-day cycle (with a 10-day rest period per cycle). Among the drug toxicities are thrombocytopenia (28%), fatigue (12%), peripheral neuropathy (12%), neutropenia, anemia, vomiting, diarrhea, limb pain, dehydration, nausea, and weakness[30,31]. Intravenous bortezomib may precipitate hypotension in patients with a history of syncope and hypertension. Congestive heart failure and prolonged QT interval has been reported.

Carfilzomib and Ixazomib are second generation proteosome inhibitors. They have been licensed for patients with MM who have had at least two prior treatments, including bortezomib and an immunomodulatory agent. Ixazomib can be administered orally. They are associated with thrombocytopenia, cardiac, pulmonary and renal toxicity[32,33]. Furthermore, peripheral sensory neuropathy may be brought on by ixazomib.

A dramatic evolution has taken place in treatment of MM with an explosion of new drugs that have clinical activity. Daratumumab is a CD38-directed cytolytic antibody indicated for the treatment of adult patients with multiple myeloma:
• As monotherapy, in patients who have failed at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug or who are double-refractory to both PI and an immunomodulatory agent.
• Along with lenalidomide and dexamethasone/h bortezomib, melphalan and prednisone in newly diagnosed patients who are not eligible for autologous stem cell transplantation.

The recommended dose is 16 mg/kg actual body weight given intravenously. The most

frequently reported adverse reactions (incidence e”20%) are infusion reactions, neutropenia, thrombocytopenia, fatigue, asthenia, nausea, diarrhea, constipation, decreased appetite, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, bronchitis, pneumonia and upper respiratory tract infection[34]. Data on its usage in paediatric and pregnant patients are lacking.

Elotuzumab, a SLAMF7-directed immunostimulatory antibody is recommended together with lenalidomide and dexamethasone for the treatment of patients with MM who have had one to three prior therapies Elotuzumab comes with the warning and precaution that it is more likely to cause infusion reactions, infections, second primary malignancies, and hepatotoxicity[35]. Data on its usage in paediatric and pregnant patients are lacking.

Isatuximab[2020] is a CD38-directed cytolytic antibody indicated for the treatment of adults with multiple myeloma:

• In combination with pomalidomide and dexamethasone, who have failed at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

• In combination with carfilzomib and dexamethasone, for cases of relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. Warnings and precautions associated with this very drug are infusion-related reactions, neutropenia, second primary malignancies and embryo-fetal toxicity[36]. The drug should be permanently discontinued should a grade 4 infusion reaction occurs. The most common adverse reactions (e”20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, diarrhoea, decreased haemoglobin, decreased neutrophils, decreased lymphocytes, and decreased platelets.

Selinexor is a nuclear export inhibitor recommended for use in combination with dexamethasone to treat adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease has proven resistant to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti CD-38 Mab[37,38].

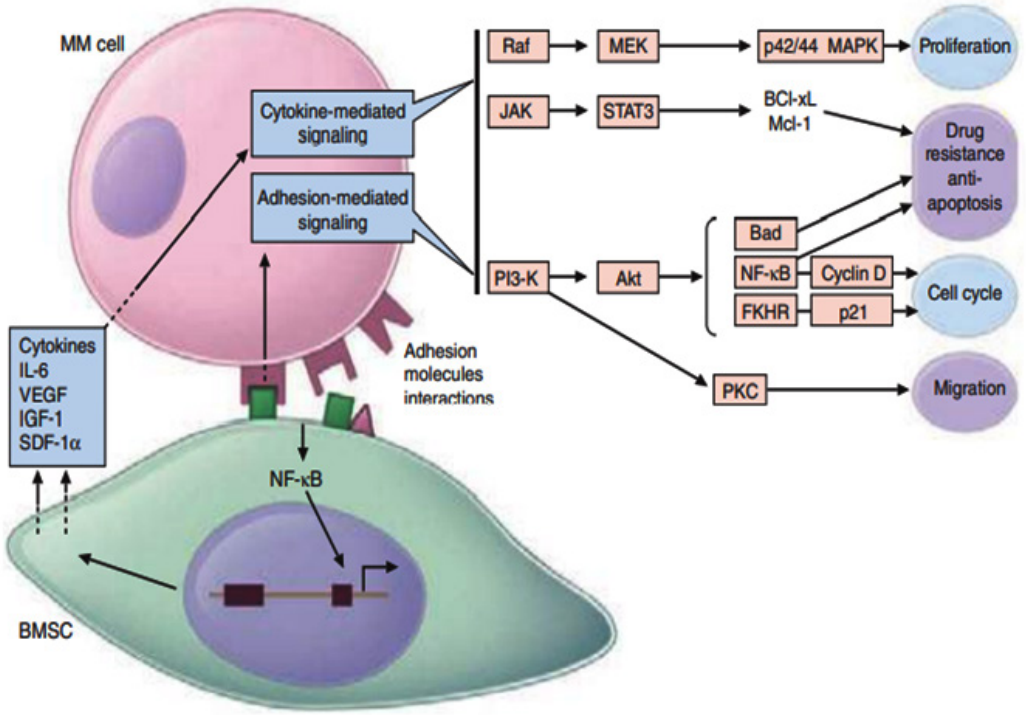

Fig. 1. Pathogenesis

Belantamab mafodotin is a B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have had at least four prior therapies, which included an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. The suggested dosage is 2.5 mg/kg administered as an intravenous infusion over 30 minutes once every three weeks. It comes with a warning of serious ocular toxicity[39], thrombocytopenia, infusion-related reaction and embryo-foetal toxicity.

Idecabtagene vicleucel[2021] is a B-cell maturation antigen (BCMA)-directed genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy. It is indicated in adults with relapsed or refractory multiple myeloma after four or more failed prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Each dose is customized using patient's own T-cells, which are harvested, genetically modified, and then infused back into the patient.

Adverse effect- cytokine release syndrome (CRS), neurologic toxicities, hemophagocytic lymphistiocytosis/ macrophage activation syndrome, and prolonged cytopenia, infections, fatigue, musculoskeletal pain, and hypogammaglobulinemia.

Ciltracabtagene autoleucel [feb 2022]

This drug has adverse effects such as cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), Parkinsonism and Guillain-Barré syndrome, pyrexia, cytokine hypogammaglobulinemia, musculoskeletal pain, fatigue, infections, diarrhea, nausea, encephalopathy, headache, coagulopathy, constipation, and vomiting.

Panobinostat is a pan-histone deacetylase inhibitor. In individuals with relapsed/refractory multiple myeloma, the combination of oral panobinostat to subcutaneous bortezomib and dexamethasone has showed favourable results[40,41]. It resulted in synergistic cell death, re-sensitization of tumour cells, progression free survival and lesser GIT toxicity. The most common adverse effect encountered was thrombocytopenia[42].

Prelixafor, a chemokine receptor 4 antagonist, is used to mobilise stem cells in patient previously treated with lenalidomide.

There are various drugs in pipeline for MM such as naked monoclonal antibodies and bispecific antibodies.

Novel therapeutics called naked monoclonal antibodies target a specific protein on the surface of MM cells, allowing the patient's immune system to abolish the targeted myeloma cells[43,44].

Felzartamab is an investigational new drug (IND) currently in phase 3 of clinical trial. This novel anti-CD38 antibody has been shown to be safe and well tolerated in patients with relapsed/ refractory MM. Administered subcutaneously, it is indicated in patients with prior exposure to immunomodulatory drugs, proteasome inhibitors, alkylating agents, and corticosteroid therapy.

Bispecific Antibodies

These are antibody-based immunotherapy, which contain two antibody fragments that have been fused together. One fragment targets the myeloma cells, in order to help the immune system locate them and the other helps immune cells by boosting their ability to find myeloma cells.[3] The majority of drugs in this class target B-cell maturation antigen (BCMA) on the myeloma cell and bind to a protein called CD3 found on the surface of T cells[45].

Elranatamab, currently under phase 2 trial is indicated in patients with relapsed/refractory MM. It is given subcutaneously in patients who are refractory to at least one drug therapy in each of the 3 major classes of medications approved for MM treatment. It has been granted fast track designation by the FDA. No dose-limiting toxicities were observed.

CONCLUSION

MM is an emerging disease. There are several drugs in pipeline like Cobemetinib, Enasidinib, Abemaciclib, Erdafitinib and Venetoclax for potential role in the treatment of MM. Pharmacogenomics and precision medicine also play a crucial role in the treatment of multiple myeloma.

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To almighty and my senior teachers

Conflict of Interest

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