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Review Article

Multiple Myeloma: Risk Factors, Pathogenesis and Relationship with Anti-myeloma Therapies

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Abstract

Multiple myeloma (MM) is the second most common hematologic malignancy with high morbidity and mortality indices. The emerging risk factors and complex pathogenic mechanisms surrounding the disease evolution are challenging. Thus, understanding these risk factors and the pathogenic basis of the disease will lead to better interventions and targeted therapies. We conduct an integrated review of the literature on MM, risk assessment, pathogenic mechanisms, and the evolution of anti-myeloma target therapies using PubMed, Medline, CINAHL, Google Scholar, African Journal Online, and Cochrane databases. The review analyze the prevalence, risk factors, and pathogenesis of MM, as well as highlights antimyeloma therapies. The literature indicates that eight risk factors are linked with MM, and two major pathogenic pathways are paramount in its evolution. We identify nine antimyeloma targeted pathways including immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, fibrin growth factor receptor inhibitors, histone deacetylase inhibitors, BCL inhibitors, immune checkpoint inhibitors, chimeric antigen receptor T-cell and B-cell maturation antigen-targeted monoclonal antibody. To holistically address the burden of MM, there is a need for in-depth knowledge of the environmental risk factors and disease pathogenic mechanisms. The cytogenetic, immunologic, and skeletal mechanisms that lead to disease evolution play significant roles in risk stratification, prognostication, and emergence of new antimyeloma therapies. A policy on MM risk assessment is therefore strongly recommended for exposed target population.

Introductory history of multiple myeloma (MM)

MM, commonly known as cancer of the bone or the immune system, is a malignant plasma cell (PC) disorder characterized by clonal proliferation of abnormal PCs in the bone marrow. It is defined clinically using the classic "CRAB" criteria of hypercalcaemia (serum calcium >11.5 mg/dL), renal failure (serum creatinine >2.0 mg/dL or estimated creatinine clearance of <40 ml/min), anaemia (haemoglobin value <10 g/dL or 2 g/dL below lower limit of normal), and lytic bone lesions (severe osteopenia, osteoporosis or pathological fracture).[1] MM was first described in 1848 by Henry Bence Jones, a chemical pathologist who first discovered myeloma proteins, previously called BJP, in the urine of MM patients.[2] PCs, which are immunologically activated B lymphocytes, are involved in the underlying pathophysiology of MM. PCs undergo somatic mutations to form abnormal PCs; hence, MM is also known as PC myeloma, a term entered in the 2008 World Health Organization (WHO) classification of malignant B-cell lymphoma.[3,4] In this disease, mutated PCs, which usually home in the bone marrow, become cancerous and multiply in the marrow. As such, MM is also known as Kahler's disease, named after the Austrian pathologist Otto Kahler who first described the condition.[5–8] MM is an end-organ disease that can cause damages to the bone, immune system, kidneys, and red blood cells. These abnormal PCs are derived from B lymphocytes, making MM a malignancy of terminally differentiated B-lymphocytes.[9]

Keywords: Multiple myeloma; Risk factors; Pathogenesis; Risk assessment; Anti-myeloma agents.

Abbreviations: ASCT, stem cell transplants; BCMA, B-cell maturation antigen target agent; BJP, Bence Jones Protein; BMM, bone marrow microenvironment; BMSC, bone marrow stromal cell; BTEX, benzene, toluene, ethylbenzene and xylene; CAR T-cell, chimeric antigen receptor; HLA, human leukocytic antigen; IARC, International Agency for Research on Cancer; IGH, immunoglobulin heavy chain; IGHV, variable immunoglobulin heavy chain ILH, immunoglobulin light chain; IMiD, immunomodulatory drugs; IR, ionizing radiation; ITIM, immunoreceptor tyrosine-based inhibitory motif; MDR/MM, multidrug resistant multiple myeloma; MGUS, monoclonal gammopathy of undetermined specificity; MM, multiple myeloma; MOAB, monoclonal antibody; PC, plasma cell; RR, relative risk; RR/MM, refractory or relapsing multiple myeloma; SMM, smouldering multiple myeloma; TIGIT, T-cell immunoglobin and ITIM domain; TME, tumor micro-environment; TSG, tumor suppressor genes; VOC, volatile organic compound; VEC, vaso-endothelial cell.

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The intriguing feature of MM is that the malignant clonal proliferating PCs produce aberrant antibodies or immunoglobin (Ig) leading to accumulation of monoclonal paraproteins in the serum, a condition known as paraproteinemia.[10] These aberrant antibodies cannot mount adequate humoral immunity, resulting in immune paresis, otherwise known as agammaglobulinemia.[11] Any class of immunoglobins namely IgG, IgA, IgM, IgD, or IgE, can be produced in MM either as intact Ig or as free light chain (i.e. kappa or lambda) or as free heavy chains (i.e. alpha, gamma, delta, epsilon, or miu).[12] MM is an insidious disease capable of causing systemic ailments and end-organ damage at its terminal stage.[13] Apart from secretory-type MM, there is a rare non-secretory-type MM in which the paraproteins are not found in the plasma or urine.[12]

Prevalence of MM

MM accounts for 1–2% of all cancers and 10–15% of hematological cancers.[14,15] MM is the second most commonest hematologic malignancy after non-Hodgkins lymphoma with an incidence rate of about 7.8 per 100,000 adults per year in the United Kingdom.[16] MM is more common among males, with a male to female ratio of 2:1.[14–17] The black race is more prone to suffer MM compared to their white counterparts.[18] The median age of individuals diagnosed with MM ranges from 60–65 years among Caucasians, and a relatively lower age in developing countries.[16] MM has a 3–5% familial tendency among family members and spouses with HLA-Cw2 and HLA-Cw5.[19]

Risk Factors of MM

1. Idiopathic MM: Like other idiopathic cancers, the definitive cause of MM is unknown. However, the risk factors that would be used for MM in this context have been shown to have key attributes like associations, predispositions, exposures, and directionalities, including host and environmental factors.[20] These factors will be discussed as risk factors versus causal inferences of MM below.
2. Familial predisposition: Genetically, MM is divided into two major karyotypes: hyperdiploid (commoner) and non-hyperdiploid MM.[21] However, studies have shown that there is a familial tendency of MM among members with human HLA (i.e. HLA-Cw2, HLA-Cw5) and other germline mutations.[19,21] Beside genetic variants, epidemiological studies have also revealed a familial risk.
3. Immune disorders: Immune-compromised conditions such as HIV/AIDS, bone marrow transplant, and organ transplantation have been linked to monoclonal gammopathy.[17,22–27] Autoimmune disorders such as pernicious anemia and ankylosing spondylitis have been linked with MM.
4. Environmental and occupational hazards: It is believed that there are hazardous agents that could predispose one to MM upon exposure. These potential environmental or occupational hazards include benzene, toluene, ethylbenzene and xylene (BTEX), which are known predisposing agents for blood and lung cancers. These are the most common volatile organic compounds (VOCs) that enter the body through inhalation (of outdoor/indoor air drops), ingestion, and skin contact. Benzene is an organic solvent used in the production of synthetic materials and consumer products such as rubber, plastics, nylon, insecticides, and paints. Toluene is a solvent used in the production of paints, coatings, gums, oils, and resins. Ethylbenzene can be used as a gasoline and aviation fuel additive. It is also a useful solvent for pesticide and ink production. Xylene is used in printing, rubber, and leather industries. According to the International Agency for Research on Cancer (IARC) classification, benzene is a category-1 carcinogenic VOC which has been found to induce MM in petrochemical workers. A periodic assessment of the Threshold Value- Time-Weighted Averages (TV-TWAs), Target Hazard Quotients (THQs) of these VOCs and their metabolites in exposed individuals and the environment will help in risk assessment of these potentially carcinogenic substances.[28–37] In addition, people working in agriculture, food processing, and chemical industries have an increased relative risk (RR) of 1.8 for developing MM. The RR is higher for people exposed to petrochemicals (RR = 3.7), asbestos (RR = 3.5) and laxatives (RR = 3.5). Prolonged use of permanent black hair dye for several years has also been shown to carry a very high risk to MM (RR = 4.39) and Non-Hodgkin Lymphoma (RR = 4.37) according to an American Cancer Society prospective mortality study.[38,39]
5. Chemical hydrocarbons: Exposure to chemicals such as dioxin, herbicides, and pesticides has been causatively linked to precursors of MM, such as monoclonal gammopathy of undetermined specificity (MGUS). These chemicals are synthetic products of BTEX.[31,40]
6. Ionizing radiation (IR): Exposure to IR from nuclear power stations or nuclear bombs has been linked to MM. A typical example is in the atomic bombing of Hiroshima and Nagasaki of Japan during World War II (1945) where about 29 of the 109 000 survivors of the bombing died of MM.[38,41,42]
7. Plasma cell dyscrasias: The first on this list is MGUS, a premalignant PC disorder with 1% risk of progression to MM per year. MGUS is followed by smouldering multiple myeloma (SMM), an asymptomatic disease with a 10–20% risk of transformation to MM per year.[43–48]
8. Infective agents: Chronic antigenic stimulation by infective agents, such as HIV,[49] Ebstein-Barr virus,[50,51] mutated cytomegalovirus,[52] hepatitis C virus,[53] Kaposi Sarcoma Herpes Virus (also known as human herpes virus-8)[54–56] and others, has been associated with MM.

Pathogenesis of MM

The B-cell lymphocyte immunoglobulin is made up of two parts, namely the heavy chain [also known as the immunoglobulin heavy chain (IGH)] and the light chain [also known as the immunoglobulin light chain (IGL)]. The IGH chain has two terminal regions: the C-terminal region (constant region) and the highly variable N-terminal region (variable region or IGHV). The IGHV locus is made up of three separate gene elements: the Variable (V or Vh) element made up of 184 variable genes (of which 55 are functional); the Diversity (D) element made up of 38 diversity genes (of which 24 are functional); and the Joining (J) region made up of nine joining (J, or Jh) regions (of which six are functional). The VDJ cluster makes up the N-terminal region of the B-cell IGH. The VDJ clusters are an important B-cell receptor gene segment.[57] The VDJ clusters undergo recombination to combine unique germlines encoding sequences in the production of a diverse spectrum of functional antibodies. A normal B cell goes through a series of recombinations with the VDJ clusters of its IGHV genes to generate a diverse spectrum of its functional antibody. They are the core determinants of the immunogenicity or immune diversity of a B-cell. When this B cell enters into a lymph node, it interacts with an antigen to differentiate into a short-lived PC that lives for about

Table 1. mSMART risk stratification of myeloma by cytogenetic abnormalities[64,66]

	Standard Risk	Intermediate Risk	High Risk
Karyotypes (FISH)	Hyperdiploidy; Trisomy; t(11;14) CCND1; t(6;14) CCND3	Hypodiploidy; Monosomy; del 13q ; t(4;14) FGFR3	del 17p; t(14;16) NSD2/WHSC1, c-maf; t(14;20) c-mafB
Incidence (%)	75	15	10
Median OS (years)	8–10	4–5	3

del: deletion; mSMART: Mayo Stratification for Myeloma and Risk-Adapted Therapy; OS: Overall Survival; t: translocation

three days. A PC is an immunologically activated B-lymphocyte that produces antibody.[58–60]

However, in MM, the circulating clonotypic B cells undergo IGH VDJ rearrangement, which is used as a diagnostic for the malignant clone of PCs seen in MM. A myeloma cell is an activated postgerminal center B-cell (PC) that has undergone repeated rounds of somatic mutations (hypermutation) and translocation (IGH switching) of the IGHV genes with selection for those with increased antigen affinity to become long-lived memory B-cells that home to the bone marrow. MM is therefore a tumor comprised of these long-lived PCs. The myeloma cell is usually confined to the BM but may occasionally be seen in the peripheral blood.[61–63]

The development of MM is a multi-step process that has two major stages: initiation stage and progression stage.

1. The initiation stage involves the origin of chromosomal (karyotypic) and immunophenotypic changes. The chromosomal changes could be numerical (aneuploidy) and/or structural karyotypic changes.
   a. Numerical karyotyping: There are two major numerical karyotypic abnormalities in MM: hyperdiploid and non-hyperdiploid (hypodiploidy) variants. Hyperdiploid variants account for about 55–60% of primary MM tumors and are characterized by hyperdiploid karyotypes with a chromosomes range of 48–78 and trisomies (extra copies of chromosomes) of odd numbers including 15, 9, 5, 19, 3, 11, 7, and 21, in order of decreasing frequency. This karyotype is typically the IgG-kappa type with bone involvement. In contrast, non-hyperdiploid variants account for the remaining 40–45% of primary MM tumors and are characterized by hypodiploid karyotype or near tetraploid chromosome numbers (chromosomes fewer than 48 or more than 74) including loss of chromosomes (monosomies) 8, 13, 14, 17, and X.[21] Chromosomal translocation (TC) is more common with the non-hyperdiploid variant. The hyperdiploid karyotype carries better prognosis, provided there is no deletion of chromosomes 13 (RB1 gene and miRNA-15A/16-1 cluster dysregulation) and 17 (involving TP53) or chromosome 1q21 amplification.[27,62]
   b. Structural karyotyping: Structural chromosomal changes in MM have to do with primary IGH gene TCs. There is increased frequency of unbalanced TC in the switch region of the IGH gene involving large arrays of chromosome partners. About 60% of MM cases undergo IgH switching TCs while the remaining 40% are unidentified.[64] Chromosome 13 monosomy (also known as Monosomy 13) is found in about 90% of MM cases. It is more common than interstitial deletion and 13q TC. According to comparative genomic hybridization reports, Monosomy 13, IGH gene switch TC, and 8q (c-myc oncogene) abnormalities are detected in 80–90% of MM cases. The frequency of 13q loss increases with disease stage. This could be an early event in MM.[38,65]
      i. Currently, MM can be stratified into three risk categories based on the cytogenetic abnormalities: standard-, intermediate- and high-risk categories. The standard-risk karyotype includes hyperdiploid variant, t(11;14) and t(6;14) while the intermediate-risk category includes hypodiploid variant, del 13q, and t(4;14). The high-risk category includes del 17p, t(14;16) and t(14;20). The incidence of standard-risk karyotype is 75% with a median overall survival rate of 8–10 years, while that of the high-risk karyotype is 10% with a 3 year median overall survival interval (Table 1).[27,38,66]
      ii. Immunophenotypic changes such as CD126, CD38, and CD138 overexpression are useful diagnostic endpoints in MM. Others include CD56+ and CD19- expression. The normal PC is CD19+ and CD56-. Proliferative myeloma cells express more CD45+ cells than non-proliferative MM. Proliferative myeloma cells are less mature, highly proliferative, and IL-6 responsive (VLA-5 or CDw49e –ve cells). Non-proliferative cells are mature cells with high M-protein production capacity. This immunogenicity property has been used as a therapeutic approach in the development of effective monoclonal antibody (MOAB) target agents (also known as antibody drug conjugates) for MM management. These include Daratumumab and Isatuximab (anti-CD38 MOAB therapies),[67] Indatuximab Ravtansine (MOAB-linked cytotoxic agent that specifically targets CD138-expressing cells,[68–71] Siltuximab (anti-IL-6 monoclonal antibody target therapy),[72] and Elotuzumab (immunostimulatory MOAB targeting signalling lymphocyte activation molecule F7 (SLAMF7 or CD319), a cell surface glycoprotein CD2 subset-1 usually expressed by myeloma cells in the bone marrow for adhesion to bone marrow stromal cells (BMSCs).[73,74] MOAB target therapy could be useful as either monotherapy or in combination with other conventional antimyeloma agents to manage relapse or refractory MM (RR/MM).[69–71]
2. Progression stage: Here clonal PCs undergo additional changes to become long-lived or immortal PCs.[61] This stage has two events that involve PCs and the bone marrow microenvironment (BMM).
   a. PC events include secondary IgH TCs (i.e. c-myc proto-oncogenes increased expression, and transcription), p53 mutation or deletion, high BCL-1 and 2 overexpression which inhibit apoptosis and promote PC immortalization. The most frequently mutated genes described in MM are KRAS (25%), NRAS (20%), FAM46C (11%), DIS3 (11%) and TP53 (8%).[64,75,76]

      In addition to somatic mutations, epigenetic aberrations play a significant role in supporting MM pathogenesis. This refers to those mechanisms that control y act against MM cells in the BMM. gene expression via chromatin remodelling that could be hereditary even in the absence of DNA sequence changes. Epigenetic aberrations in MM involve

DNA methylation and histone modification.[77] Epigenetic mechanisms work by adding methyl groups at the promoter regions of the DNA in order to silence the target genes. Although global DNA hypomethylation has been demonstrated in human cancer development, the aggressive subtypes of MM could be detected by multiple loci of hypermethylated DNA. DNA methylation could lead to miRNA inactivation and inhibition of tumor suppressor genes (TSG). Inhibited TSGs in MM include GPX3, RSBPI, SPARC, and TGFBI. Inactivation of these genes is higher as MM progresses to PC leukaemia. Another epigenetic component that is abnormally expressed in MM is the t(4;14) karyotype MM SET domain (MMSET) also known as NSD2 or WHSC1, a histone modifying gene identified in Wolf-Hirschhorn Syndrome. The WHSC1 brings about the methylation of H3 and H4 leading to formation of H3K36-dimethylation (H3K36me2) and H4K20-trimethylation (H4K20me3). These aberrant epigenetic products favor histone deacetylase-1,2 and histone demethylase (LSD-1) functions, which ultimately leads to myelomatogenesis. The accumulation of H3K36-me2 levels lead to MM cell growth and disease progression through transcriptional activation of oncogenes.[78–80] Other important genes that undergo methylation in MM include p16, o6-methyl guanine methyl transferase (MGMT) ink4A, death-associated protein kinase (DAPK) and E-cadherin (ECAD). The promoter hypermethylation of MGMT is more associated with extramedullary MM than other genes.[81] Myelomatogenesis has also been associated with low folate intake and MTHFR (methylene tetrahydrofolate reductase) polymorphism (MTHFR 677CC) with higher prevalence of p16 hypermethylation.[82]

b. BMM events include mutual interactions that affect the number and function of both malignant cells and normal BMSCs. The BMM includes the extracellular matrix and five types of stromal: fibroblasts, osteoblasts, osteoclast, vaso-endothelial cell (VEC), and lymphocytes. BMM interactions are mediated by cytokines and adhesion molecules.[21,38,62] The homing of MM cells to the bone marrow involves selective adhesion to bone marrow endothelial cells, transendothelial migration, and adhesion to BMSCs via SDF-1 and IGF-1. The homing of myeloma cells to bone marrow VECs via VLA-4 integrin/VCAM -1 interaction induces paracrine upregulation of cytokines such as IL-6, VEGFs, b-FGF, IL-1b, IL-11, TNFs, TGF-beta, and RANKL by BMSCs. The stromal-MM cell interactions form the therapeutic basis for the therapeutic use of IMiD agents (i.e., thalidomide, lenalidomide, pomalidomide) in downregulating IL-6 and VEGF in MM. They act against MM cells in theBMM.[83,84] IL-6 production occurs via activation of the transcription factor NF-kB. Its production triggers proliferation of myeloma cells and protects them against dexamethasone-induced apoptosis. NF-kB activation is responsible for the production of other growth factors and adhesion molecules such as VEGFs, VCAM-1, and E-selectin by BMSCs and myeloma cells. Inactivated NF-kB is located in the cytoplasm where it is bound to its inhibitor IkB. Its activation involves a sequence of processes involving activation of IkB-kinase enzyme, which leads to its phosphorylation (IkB-phosphatase). The IkB-phosphatase catalyzes the ubiquitination and degradation of IkB by proteasome, leading to dissociation and translocation of NF-kB, originally bound to the IkB in the cytoplasm, to the nucleus. The nuclear translocation of NF-kB is important for the production of molecules crucial for MM survival.

The above pathway forms the basis of the antimyeloma effect of drugs such as dexamethasone and proteasome inhibitors (i.e., bortezomib), which inhibit NF-kB production.[85,86] Current studies have shown that the TME plays a strategic role in the survival and progression of myeloma cells through protecting malignant cells against antitumor therapy.[87] The inflammatory mesenchymal stroma cells (iMSC), osteoclasts, osteoblasts, myeloid, and lymphoid cells in the bone marrow create a unique environment that favors myeloma cell immune evasion and disease progression. These cells are able to carry out these functions by transcribing myeloma survival factors through CCL2-CCR2 interactions. These interactions lead to paracrine secretion of high levels of chemokines (cytokines as mentioned above) that propagate the disease process and antitumor responses through activation of matured CD15+ neutrophils and classical CD14+ monocytes at their CXCR1 and CXCR2 receptors, respectively.[88] The hallmark of BMM interaction is induction of angiogenesis by IL-6. The precise role of this in MM propagation is not well-established, but it has been found to be related to increase in growth factors such as VEGF, FGF-b, and other similar factors responsible for the survival of myeloma cells. There is also suppression of T-cell-mediated immune responses in MM due to increased and reduced IFN-alpha and gamma production, respectively.[89]

The bone disease is the hallmark of MM because it reduces quality of life and increases disability adjusted life years, morbidity, and mortality of those with MM. The skeletal related events are brought about by activation of osteoclasts and inhibition of osteoblast differentiation. This process is mediated though the signalling of several intercellular and intracellular signalling cascades, including RANK/RANKL/OPG, Notch, Wnt, RUNX2, EphrinB2/EphB4, and TNF pathways, as well as signalling molecules such as DKK1, sclerostin, periostin, osteopontin, GFI1, BMPs, TGFβ, activin A, annexin II, adiponectin, BTK, SDF1a, chemokines, and interleukin.[90] Osteoclast activation occurs where there is an increased RANKL/OPG ratio and increased levels of IL-6, IL-11, MIP-1 alpha, TNFs, and IGF. The increased RANKL/OPG ratio is occasioned by increased RANKL expression and reduced OPG levels. Bisphosphonates block the activation cascade that leads to osteoclast-induced osteolysis in MM through inhibiting the RANK/RANKL/osteoprotegerin pathway.[91–93] Inhibition of osteoblast differentiation is RUN-X2-mediated and is due to increased levels of IL-3, IL-7, DKK-1 and other cytokines. Increased IL-7 levels have been found in bone marrow PCs of MM patients. Therefore, targeting RUNX2, GFI1, and IL-7 might be a strategic approach to curb MM-induced bone destruction.[94,95]

Antimyeloma targeted therapies derived from disease pathways

Although there is a dramatic therapeutic evolution in the management of MM, the disease remains incurable. T-cell exhaustion (evidenced by lymphodepletion, deterioration of its function) and TME suppression (as evidenced by immune evasion) have been implicated in myeloma disease progression. The immunotherapy and most novel antimyeloma interventions work by interfering with T-cell function and the TME.[96] TME suppression, which characterizes myeloma disease progression, renders immunotherapy ineffective. Basically, the two modes of treatment of MM include pharmacologi-

Table 2. Common target anti-myeloma agents with their ending acronyms and mode of actions

S/N	Anti-myeloma Target Family	Ending Acronym	Mechanism of Action	Examples
1	Immunomodulatory (IMiD) agents	-MIDE	Anti-angiogenesis via downregulating VEGF and IL-6.	Thalidomide Lenalidomide Pomalidomide[82,83]
2	Proteasome Inhibitors (PIs)	-MIB	Inhibit NF-kb production via prevention of ubiquitination and degradation of Ikb.	Bortezomib, Carfilzomib, Isaxomib, Marizomib, Oprozomib[84]
3	FIBRIN GROWTH FACTOR (FGFR) INHIBITOR	-NIB	Inhibits tyrosine kinase involved in VEGR and PDGF required in tumor proliferation (FBFRI).	Dovitinib
4	HISTONE DEACETYLASE INHIBITORS (HDACI)	-STAT	Prevents deacetylation of histone and non-histone protein.	Panobinostat, Vorinostat, Rocilinostat,
5	BCL INHIBITOR	-CLAX	Proapoptotic and anti-fibrotic agent. Reduces platelet lifespan causing thrombocytopenia.	Navitoclax
6	Monoclonal Antibody (MOAB) AGENTS	-MAB	Antibody drug conjugates	Elotuzumab (SLAMF7 O or CD319) immunostimulatory agent;[72,73] Daratumumab (anti-CD38);[67] Indatuximab Ravtansine (anti-CD 138);[68–70] Siltuximab (anti-IL-6)[71]
7	Immune Checkpoint receptors inhibitors.	TIGIT blockers	They restore primary function of T-cell which is recognition and elimination of MM cells.	
	CAR T-cell		Cytogenetic modification of MM protein T-cells using BCMA as target.	Idecabtagene Vicleucel -targeted against MDR RR/MM[98,99]
	BCMA-target MOAB		Targets overexpressed BCMA in MM	Belantamide mafodotin- more convenient than CAR T-cell therapy in adult[98,99]
8	STEM CELL TRANSPLANT		ASCT re-establishes immune equilibrium, prevents immune escape.	ASCT[95,96]
9	Tumor vaccine: Vaccination against MM is the proposed future direction in the disease management. Targeting RUNX2, GFI1 and IL-7 might be a strategic approach of curbing MM-induced bone destruction.			

ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CAR T-cell, chimeric antigen receptor T-cell; CD, cluster of differentiation; GFI1, growth factor independence 1; IL-6, interleukin-6; IL-7, interleukin-7; MDR, multidrug resistance; MM, multiple myeloma; MOAB, monoclonal antibodies; NF-kb, nuclear factor kappa B; PDGF, platelet-derived growth factor; RR/MM, refractory/relapsed multiple myeloma; RUNX2, runt-related transcription factor 2; SLAMF7, signaling lymphocytic activation molecule family member 7; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; VEGF, vascular endothelial growth factor.

cal (i.e. conventional cytotoxic chemotherapies, immunostimulatory such as IMiDs drugs and elotuzumab, immune check point inhibitors, and other target therapies) and stem cell transplant (ASCT) interventions. The primary function of T-cells in MM is to recognize and eliminate myeloma cells (i.e. via functionally active CD8+ T-cell) and subvert these cells during myeloma disease progression. However, ASCT intervention has the ability to re-establish immune equilibrium, prevent immune escape, and create a favorable environment for immunotherapy (i.e. bispecific antibodies or CAR T-cells) in transplant-eligible MM patients.[96,97] The definitive therapeutic interventions for MM usually involve a combination of standard target therapies, which act at specific pathways in the pathogenesis and biology of the disease. These target therapies take their origins from different pharmacological groups. The ending rhyme (acronym) for each target therapy is used to identify the drug family of origin. The following acronyms are useful in identifying the classification of antimyeloma target therapies: the 'MIDE' acronym represents the IMiD family (i.e., thalidomide, lenalidomide, pomalidomide); the 'MIB' acronym represents proteasome inhibitors (such as botuzemib, carfilzomib, isaxomib, marizomib, and oprozomib); the 'MAB' acronym represents the monoclonal antibody target agents (such as elotuzumab, daratumumab, siltuximab, indatuximab, and isatuximab); the 'NIB' acronym represents the FGFR inhibitor (such as dovitinib); the 'CLAX' acronym represents BCL inhibitors (such as navitoclax); and the 'STAT' acronym represents the histone deacetylase inhibitors (such as panobinostat, vorinostat, and rocilinostat) (Table 2).

The RR/MM is the consequence of myeloma disease progression (TME suppression) which is evidenced by T-cell exhaustion, TIGIT immune checkpoint receptor upregulation (the receptor which negatively regulates T-cell function), inhibitory receptor expression on CD8+ T-cells, CD226 (DNAM-1) downregulation, and upregulation of other inhibitory receptors. The emerging antimyeloma target therapies indicated for MDR/MM include TIGIT immune checkpoint inhibitors, CAR T-cell, and BCMA target agents. The TIGIT immune checkpoint inhibitors are made to restore the primary function of T-cells by downregulating inhibitory receptor expression on CD8+ T-cells and upregulating CD226 (DNAM-1).[98] CAR T-cell therapy such as Idecabtagene Vicleucel is a promising highly-specialized therapy that involves a cytogenetic modification of the patient's own T-cells to attack the MM cells using a target called BCMA. It is indicated for RR/MM, especially those who have refracted for at least four prior treatments with or without relapse (MDR/MM or RR/MM) involving triple class regimens of IMiD, proteosome inhibitors, and anti-CD38 MOAB, a condition commonly known as triple class refractory MM.[99,100] The current strategies for targeting BCMA in RR/MM involve antibody-drug conjugates known as BCMA-target therapies. The BCMAs are specifically overexpressed in RR/MM. Patients who use BCMA-target therapies are likely to do better earlier than those using CAR T-cell therapies. Belantamide mafodotin is an example of a BCMA-targeted MOAB therapy that is approved by FDA.

Belantamide mafodotin is better tolerated in older and frail patients who do not want to use CAR T-cell or to be hospitalized to receive a dose of 2.5 mg/kg intravenously once every 3 weeks. The adverse effects of Belantamide mafodotin include ocular and hematologic toxicities.[101–104] ASCT is another definitive therapeutic intervention for newly diagnosed MM transplant-eligible patients. This mode of therapy is aimed at long-term disease control just like the target therapy.[105] In addition, MM patients can benefit from involved field radiotherapy. Radiation therapy is an effective adjuvant therapy for myeloma bone disease and solitary plasmacytoma.[106,107]

Future directions

The current antimyeloma target therapies are derived from emerging risk factors and the complex pathogenic mechanisms of MM. Moving forward towards addressing the burden of MM, these risk factors and the underlying pathogenic pathways must be translated into preventive and curative interventions that can achieve effective control. These could be achieved by exploring the following performance tools:

A risk assessment policy on prospective risk factors of MM in the environment, work place, and occupations and industries where chemical exposures are strongly anticipated: Chemical exposure in this context is defined as exposure to agriculture, food, air pollutants, petrochemical industries, farmers exposed to insecticides, individuals exposed to organic solvents, and long-term exposure to hair dyes. Risk assessment in this context is by use of the four-step-approach, which includes hazard identification, dose-response assessment, exposure assessment and risk characterization.

Strategically reverse each of the evolving pathogenic pathways (cytogenetic, skeletal, and immunologic) using respective target therapeutic agents. Targeted antimyeloma agents could be developed that could reverse the cytogenetic aberrations in high-risk, intermediate-risk, and standard-risk type MM. For example, focus could be placed on target therapies that could reverse skeletal-related events (orthopedic complications) in MM via activating osteoblast differentiation and inhibiting osteoclast differentiation. Impaired immune microenvironment and T-cell senescence have been implicated as major problems in MM underlying relapses and extramedullary disease progression. Future exploration on intervention involving nanoparticles that could reverse T-cell senescence and enhance immunogenic cell-death of MM cells will play a significant role in MM tumor eradication.

Tumor vaccine development: Future exploration of immunization as a preventive strategy against MM is strongly recommended. Vaccination against MM will be beneficial for disease management. Targeting RUNX2, GFI1, and IL-7 might be a strategic approach of curbing MM-induced bone destruction.

Conclusions

The emerging risk factors and complex pathogenic mechanisms surrounding MM disease evolution are challenging. Hence, understanding these risk factors and the pathogenic basis of MM will potentially yield interventions using target therapies. To holistically address the burden of MM, there is a need for in-depth knowledge of the environmental risk factors and disease pathogenic mechanisms. The cytogenetic, immunologic, and skeletal pathways that lead to disease evolution play significant roles in risk stratification, prognostication, and emergence of new antimyeloma target therapies. A policy on MM risk assessment and management is therefore strongly recommended for exposed target populations.

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Conflict of interest

The authors declare no conflicts of interest related to the authorship and publication of this article.

Author contributions

OCN was the sole author of this manuscript, and contributed to the development of the study, data analysis, writing and revision of the article, and gave approval of the final version submitted for publication.

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