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Review

Multiple Myeloma: What Do We Do About Immunodeficiency?

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Abstract

Multiple myeloma (MM) is an incurable hematological malignancy. Immunodeficiency results in the incapability of immunity to eradicate both tumor cells and pathogens. Immunotherapies along with antibiotics and other anti-infectious agents are applied as substitutes for immunity in MM. Immunotherapies including monoclonal antibodies, immune checkpoints inhibitors, affinity-enhanced T cells, chimeric antigen receptor T cells and dendritic cell vaccines are revolutionizing MM treatment. By suppressing the pro-inflammatory milieu and pathogens, prophylactic and therapeutic antibiotics represent anti-tumor and anti-infection properties. It is expected that deeper understanding of infection, immunity and tumor physio-pathologies in MM will accelerate the optimization of combined therapies, thus improving prognosis in MM.

Key words: immunodeficiency, multiple myeloma, immunotherapy, antibiotic

Introduction

Multiple myeloma (MM) is a heterogeneous malignancy developed with the accumulation of malignant plasma cells within bone marrow. Common complications of MM are infections, anemia, renal failure, hypercalcemia and osteolytic bony lesions. Median age of MM patients at diagnosis is 69 in the USA and 59 in China. Patients with MM are expecting better prognosis in more recent decades. With the introduction of proteasome inhibitors and immunomodulatory agents, MM median overall survival is now beyond 60 months.[1] Notwithstanding the improved early-term survival, MM remains an incurable disease. From precancerous monoclonal gammopathy of uncertain significance, active stage, to plateau stage, MM will eventually and inevitably progress into relapsing stage and drug resistant stage. Repeated infections, development of drug resistance and disease progression in MM are all closely associated with the acquisition of immunodeficiency. [2–5]

Immunodeficiency principally results in the incapability of immunity to eradicate tumor cells and pathogens. The duality of immunodeficiency in MM patients is essential in understanding the latent interactions between malignant cells, pathogenic microorganisms and the host immunity, especially provided that we are to develop promising drugs to achieve curative potential. This review outlines the mechanisms and up-to-date clinical applications of several therapeutic strategies targeting immunodeficiency. We focus primarily on immunotherapies, especially novel treatment options of monoclonal antibodies and chimeric antigen receptor T cells, and anti-infectious agents, as substitutes for immunity to eradicate pathogens and malignant cells, respectively. Note that because of the same immunodeficiency background infections and myeloma share, a successful treatment on one can bring prospect for the other, which is demonstrated markedly in vaccines and antibiotics for MM.

Immunodeficiency in MM

The dysfunctional replication of plasma cells,

chemotherapy-induced granulocytopenia and the high-dose administration of dexamethasone are all responsible for immunodeficiency, which involves in tumor evasion from the immune response.[2,6–9] Both humoral immunity and cellular immunity are impaired in concordance with abnormities of B cell, T cell, dendritic cell (DC) and natural killer (NK) cell *et al.*, in terms of quantity and function[2,10–16] It was demonstrated that serum β-2-microglobulin was significantly higher in the MM subgroup with a high ratio of CD4+ cells to CD8+ cells in peripheral blood than in the subgroup with a normal ratio ($P < 0.05$).[12] Indeed, MM with a dismal long-term survival was accompanied with less-proliferated cytotoxic T-cell clones, lower Th17 cells and higher T-regulatory cells (Tregs).[17] Besides, DC function could be inhibited by profound immune dysregulations of various immune agents including TGF-β, IL-10, IL-6, PGE2 within myeloma microenvironment.[18,19] Abused activation of programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) immune checkpoints also caused undesirable immunodeficiency in MM.[20,21] B7-H1 expression was upregulated on tumor cells, thus inducing T-cell suppression, tumor progression and drug resistance.[22,23] As for CTLA-4, it has been discovered in a polish cohort of 580 people that CTLA-4 gene polymorphism is relevant to susceptibility to MM. The frequency of CTLA-4c.49A>G[G] allele was much higher in the MM patients than in the controls ($p=0.03$, OR=1.31, CI=1.03-1.68).[24] CTLA-4 polymorphisms also have influence on outcomes of treatments involving bortezomib, the mechanism of which still waits to be fully elucidated.[25]

In abridged, we enumerate major immunodeficiency mechanisms in MM of recorded clinical significance: (1) abnormal expression of specific antigens on malignant cells;(2) enhanced expression of immune checkpoint inhibitory ligands by plasma cells;(3) T-cell abnormities;(4) dendritic cell dysfunctions;(5) immune microenvironment dysfunctions. Congruently, several therapeutic strategies targeting immunodeficiency are later addressed.

Immunotherapy

The fundamental basis for immunotherapy is to ameliorate the impaired immunity in MM through simulation or immune supplement. Apart from Arkansas total therapy protocols,[26] allogeneic stem cell transplantation (allo-SCT) is generally believed to be the only curative therapy for MM, despite the fact that high treatment-related mortality limits its use.[17,27,28] Notion that MM regresses by immune enhancement strongly justifies the application of immunotherapy.[29] In accordance with the immunodeficiency mechanisms, various treatments are subsequently elucidated to address this dilemma: (1) monoclonal antibodies (mAbs);(2) immune checkpoints inhibitors;(3) affinity-enhanced T cell therapies and chimeric antigen receptor T cell therapies;(4) DC vaccines; (5) immunomodulatory drugs.

Monoclonal Antibody

The monoclonal antibodies (mAbs) are among the most promising therapies for patients with hematological or solid malignancies.[30] mAbs take advantage of the unique immunoglobulin expression by malignant cells. They specifically target functional surface antigens or immune agents, leading to different mechanisms that keep tumor at bay. The key step toward monoclonal antibody treatment is to identify suitable surface antigens. Ideally, a target for mAb therapy should be exclusively or predominantly expressed on most MM cells or other target cells in order to minimize substantial on-target off-tissue toxicity and maximize efficacy.

MAbs have shown encouraging ability to overcome MM resistance after traditional therapies.[31] Intriguingly, the anti-CD38 mAb daratumumab and anti-CS1 mAb elotuzumab were approved by FDA as breakthrough drugs for the treatment of MM in 2015. [32,33] Daratumumab (HuMax-CD38, Genmab) is a human IgG1κ mAb that binds to the CD38 epitope on MM cells.[34] Main anti-myeloma mechanisms of daratumumab exhibited in preclinical studies include antibody-dependent cellular cytotoxicity (ADCC), omplement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP) and cross- linking apoptosis.[35,36] In CASTOR phase 3 Trial (NCT02136134), the addition of daratumumab to the regimen of bortezomib and dexamethasone resulted in a significantly higher rate of 12-month progression-free survival (60.7% vs. 26.9%), as was the rate of overall response (82.9% vs. 63.2%, $P<0.001$).[37] In another phase 3 trial POLLUX (NCT02076009), the addition of daratumumab to the regimen of lenalidomide and dexamethasone demonstrated a significantly higher rate of overall response among patients with relapsed or refractory MM (92.9% vs. 76.4%, $P<0.001$).[38] Another mAb target, CS1, a member of the CD2 subset of immunoglobulin superfamily,[39] was expressed on NK cells and in more than 97% of MM patients.[40] The first-in-class humanized IgG1 anti-CS1 mAb, elotuzumab, was demonstrated to mediate ADCC, inhibit CS1-mediated MM cell adhesion and directly enhance NK cell cytotoxicity in the bone marrow milieu.[40,41] A combination of mAb elotuzumab, lenalidomide and dexamethasone was reported to induce an

over-12-month progression-free survival in 68% patients with relapsed or refractory MM, as compared to 57% in patients who received only lenalidomide and dexamethasone. As for 24-month progression free survival, the rates were 41% and 27%, respectively. Incidence of infusion reaction was 10%, with 29 of 33 patients under grade 2.[42] Some of the most promising antigens and monoclonal antibodies for MM along with their mechanisms and clinical applications are described in this review. (see Table 1)

Immune Checkpoint Inhibitor

Immune checkpoints refer to an immune regulatory system which plays a crucial role in tumor immune evasion. CTLA-4 and PD-1 are both immune checkpoint receptors on T cells. The engagement by their cognate ligands B7-1 (CD80)/ B7-2 (CD86) or programmed cell death ligand-1 (PD-L1)/ programmed cell death ligand-1 (PD-L2) on antigen-presenting cells leads to a temporary attenuation of T-cell activation.[43–45] Comparisons of the immune checkpoints CTLA-4 and PD-1 are generalized in Table 2.

Thus far, a subset of immune checkpoint inhibitors has been approved for therapeutic use in certain solid tumors by FDA and CFDA (China Food and Drug Administration). However, whether they have the same effect in patients with MM is not yet clear. As MM is a genetically and immunologically complex disease, it is possible that targeting only one immune checkpoint pathway will not be sufficient.[44] Low expression of PD-1 and CTLA-4, minimal numbers of infiltrating T cells and a relatively modest mutational burden are probably relevant to patients' suboptimal response to checkpoint inhibitors in MM compared with solid tumors.[46–48] The objective response rate of pembrolizumab, pomalidomide and dexamethasone was 50% in 24 patients with relapsed or refractory MM (NCT02289222).[49] What's more, a phase III randomized trial of pembrolizumab (MK-3475), lenalidomide and dexamethasone is ongoing involving 640 participants with newly diagnosed and treatment-naïve MM who are ineligible for autologous stem cell transplantation (ASCT) (NCT02579863).[50] In the same trial, adverse events grade 3 to 4 including hematologic toxicities, hyperglycemia and pneumonia were observed in 40% patients who received 28-day cycles of pembrolizumab and dexamethasone.[51] The combination of pidilizumab and lenalidomide has demonstrated acceptable safety results in 12 patients with relapsed or refractory MM.[52] Generally speaking, checkpoints inhibitors are enticing immunotherapies but unlikely to be a panacea across MM, and much remains to be done in order to maximize their therapeutic potential. (see Table 1)

Table 1. Promising targets (antigens) for CARTs and monoclonal antibodies in multiple myeloma

Surface antigens	Monoclonal antibodies/ligands	Relevant agents and pathways	Preclinical CARTs	Clinical CARTs	References
CD19	_	_	YES	YES	[104,105]
CD20	rituximab, ibritumomab, tositumomab	PAX5/BSAP	_	_	[106,107]
CD38	daratumumab, SAR650984, MOR202	CDC, ADCC, ADCP, apoptosis	YES	_	[32–36,38,108,109]
CD40	G28-5, lucatumumab (HCD122), dacetuzumab (SGN-40), 5C11,	IL-6, TNF, PI3K / AKT, VEGF	_	_	[110–113]
CD44 (serglycin proteoglycan)	ARH460-16-2	IL-6, serglycin, IGF-1	YES	_	[114–117]
CD54 (ICAM-1)	BI-505, TP15-Fc	Mac-1, LFA-1	_	_	[118–121]
CD56 (NCAM-1, Leu-19)	HuN901, lorvatuzumab mertansine (IMGN901)	several cytokines	YES	_	[122,123]
CD74	milatuzumab (hLL1), IMMU-110	HLA-DR, NF-κB, IL-8	_	_	[124–127]
CD81	_	PERK, IRE1, X-box binding protein-1	_	_	[128]
CD138 (syndecan-1)	B-B4, BT062, 4B3	NF-κB, STAT3, Dll1/Notch	YES	YES	[129–135]
CD200 (MOX1, OX-2, MRC)	samalizumab, ALXN6000	β2 microglobulin, IGF-1R, ERK	_	_	[136,137]
CD221 (IGF-1R)	IGF-1 (natural), AVE1642, linsitinib (OSI-906)	tyrosine kinase	_	_	[138]
BCMA (CD269, TNFRSF17)	EM801, GSK2857916	BAFF (TNFSF13B), APRIL (TNFSF13)	YES	YES	[58,139–144]
CD274 (PD-L1, B7-H1)	MSB0010718C, atezolizumab, MEDI4716	PD-1	_	_	[46,145–148]
CD317 (HM1-24, BST2)	GFTKO-AHM	ADCC	_	_	[149]
CD319 (SLAMF-7, CS1, 19A24)	elotuzumab (HuLuc63, empliciti)	ADCC, CS1	YES	_	[32,39–41]
IL-6	siltuximab	Ras, IL-6	_	_	[150–152]
RANKL	denosumab	Serum C-terminal telopeptide of type 1 collagen	_	_	[153]
Dickkopf-1 (DKK1)	BHQ880	IL-6, Wnt signaling	_	_	[154–156]
PD-1 (CD279)	nivolumab (MDX-1106), pembrolizumab (MK-3475), pidilizumab (CT-011)	PD-L1	YES	YES	[47,157–163]

CARTs: chimeric antigen receptor T cells; CD: cluster of differentiation; ICAM-1: intercellular cell adhesion molecule-1; NCAM-1: neural cell adhesion molecule-1; IGF-1R: insulin-like growth factor-1 receptor; BCMA: B cell maturation antigen; PD-L1: programmed cell death ligand-1; B7-H1: B7 homolog-1; SLAMF-7: signaling lymphocytic activation molecule family member-7; IL: interleukin; RANKL: receptor activator of nuclear factor-κB ligand; PD-1: programmed cell death protein-1; IGF-1: insulin-like growth factor-1; CDC: complement-dependent cytotoxicity; ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; TNF: tumor necrosis factor; HLA: human lymphocyte antigen; STAT3: signal transducers and activators of transcription-3; ERK: extracellular regulated protein kinase; BAFF: B-cell activating factor.

Table 2. Comparison of CTLA-4 and PD-1 receptors

receptor	CTLA-4	PD-1
ligands	B7-1/B7-2	PD-L1/PD-L2
mechanism	competitive inhibition of CD28 costimulatory pathway	CD28 signaling regulation
expression on Tregs	highly expressed	dispensable
involved immune phase	priming phase of T cell activation	chronic antigenic stimulation
other pathways	-	BCR signaling inhibition by recruiting SHP-2
clinical application in MM	-	in combined therapy
other clinical applications	gastrointestinal, genitourinary cancers, melanoma	broad

T-cell Therapy

T-cell therapies fall into two major categories: non–gene-modified strategies and gene-modified strategies, or affinity-enhanced and chimeric antigen receptor T cell therapies. Those therapies rely on affinity-enhanced T-cell receptors (TCRs) or chimeric antigen receptors (CARs) to recognize specific antigens.

Affinity-enhanced T-cell Therapy

Observations that affinity-enhanced T cells are more likely to be found close to tumor lay a basis for affinity-enhanced T-cell therapies. By selection and expansion of marrow-infiltrating or genetically engineered T cells, the functional avidity between TCRs and tumor antigens was enhanced.[53] Unlike chimeric antigen receptor T cell therapies (CARTs), affinity-enhanced therapies are human leucocyte antigen (HLA)-dependent and highly potentiated to recognize intracellular peptides. Nevertheless, affinity-enhanced therapies may result in HLA downregulation and deleterious off-target effects.[54, 55]

In NCT01245673, 27 patients with active and/or high-risk MM received the subcutaneous injection of MAGE-A3 Trojan peptide vaccine, poly-ICLC along with granulocyte macrophage colony-stimulating factor (GM-CSF) before ASCT. They had steady-state apheresis to have T cells collected 10 days after the injection. These T cells were depleted of monocytes, expanded, harvested and infused back to patients. High frequencies of immune responses were observed in patients.[56]

Chimeric Antigen Receptor T-cell Therapy

CARs are genetically engineered receptor- or ligand-based proteins exhibiting high, HLA-independent specificity and tumor cytotoxicity. A chimeric antigen receptor normally consists of an extracellular single-chain variable fragment derived from mAbs or a domain derived from native receptors, a spacer region, a transmembrane domain, a tyrosine-based activation domain (usually CD3 ζ) (1st generation) , and one (2st generation) or two (3st generation) intracellular costimulatory domains (e.g., CD28, OX40, ICOS or CD137).[57]

CARTs are the second step in T-cell engineering and there are currently satisfying early-stage clinical results in MM. Several targets have been under exploration, with B cell maturation antigen (BCMA) CARTs among the most promising.[58, 59] BCMA CARTs were both efficient and safe in heavily pre-treated relapsed or refractory MM according to a latest report of 16 patients. The rate of eradication of extensive bone and soft-tissue myeloma was 81%, very good partial response or complete response 63%, with severe but reversible toxicities.[60] However, one roadblock in the development of CARTs could be the lack of ideal targets. Ideally, targets for CART should be expressed on the surface of all MM cells but no normal tissues in most MM patients in order to avoid on-target off-tissue toxicity and maximize effectiveness.[61] Clinical and preclinical applications of the most promising CARTs targeting BCMA, CD19, CD38, CD138 *et al*. are listed in Table 1.

DC Vaccine

Vaccines in MM share anti-pathogen as well as direct anti-tumor potency. In the CAPiTA randomized double-blind clinical trial of 84,496 participants of age 65 years and older in the Netherlands (NCT00744263), the 13-valent pneumococcal conjugate vaccine efficacy of 45.56% was demonstrated for the first episode vaccine-type pneumococcal community-acquired pneumonia. Vaccination could also assist in the prevention of common etiologies for recurrent infections in MM patients, such as influenza, varicella, meningitis.[62] Simultaneously, vaccines became attractive in the field of cancer immunotherapy. Although mAbs have demonstrated potency in targeting malignant cells in MM, the absence of immune memory limits the durability of remissions, under the circumstances of which we are anticipating a broader application in vaccines as immunotherapies. Nevertheless, a significant drawback of ordinary anti-tumor vaccines is their efficacy instability.[63] As already emphasized, this is partially because antigen presenting cells, in particular DCs, upon which costimulatory molecules are expressed to ensure satisfactory immune response, are insufficient both in number and function.[64] In order to circumvent this problem, the

application of DC vaccines and several immune adjuvants is suggested.[65]

One research revealed that human dickkopf-1 and human heat shock protein-70 fusion vaccine could effectively elicit tumor apoptosis and prolonged survival in murine MM.[66] With regard to DC vaccines, evaluated antigen loading strategies include peptide based vaccines, genetically engineered antigen, viral/fungal vectors expressing cancer antigens and malignant cell apoptotic bodies,[67] while antigens of interest include mucin-1 (MUC1), New York-esophageal squamous cell carcinoma (NY-ESO-1), melanoma antigen family (MAGE)-A3, MAGE-C1, and receptor for hyaluronan-mediated motility receptor (RHAMM).[68,69] In a phase II clinical study, idiotype immunoglobulin-loaded DC vaccines were administered to patients intradermally. As a consequence, lower incidence of cumulative progression was observed 12 months after the first vaccination ($p= 0.099$).[70]

Immunomodulatory Drug

Immunomodulatory drugs (IMiDs) (i.e., thalidomide (α-N-phthalimido-glutarimide), lenalidomide (CC-5013), and pomalidomide (CC-4047)) are analogues with a multitude of direct and indirect anti-myeloma effects, including potent anti-angiogenesis, ADCC, immune modulatory and anti-inflammatory properties.[71,72] A leading mechanism of IMiDs in MM is the degradation of essential lymphoid transcription factors IKZF1and IKZF3 by the CRBN-CRL4 ubiquitin ligase.[73] In combination with dexamethasone or proteasome inhibitors, IMiDs represents a paradigm shift in the treatment of MM and are currently used as frontline therapy.[74] In year 2006, both in combination with dexamethasone, lenalidomide was approved for relapsed or refractory MM and thalidomide was approved for newly diagnosed MM by FDA. The FDA approval for pomalidomide in relapsed or refractory MM as a third line therapy was not issued until year 2013.[75] IMiDs are all contraindicated in pregnancy owing to proven teratogenic effects (e.g., phocomelia).[76] Other common side effects of IMiDs include fatigue, myelosuppression, peripheral neuropathy and thrombosis.[77]

Antibiotics and Anti-viral Treatment

Infection and Anti-infective Treatment

A direct consequence of immunodeficiency is the high risk of infection. The incidence rate of infectious episodes in MM was about 10 times higher than other hospitalized patients and responsible for 62.5% of early mortality in elderly patients with MM.[78,79] The infectious and re-infectious rate was 17.9% and 41.9% in 260 hospitalized patients. Risk factors of infection for those patients were female, Durie-Salmon stage IIIB, elevated serum creatinine, neutropenia, poor general condition and catheter indwelling.[80] 58% of MM patients developed respiratory infections following allo-SCT in the first 12 months after diagnosis.[81]

In this context, preemptive administration of antibiotics has been somehow widely applied in MM. Daily administration of acyclovir, valacyclovir or famciclovir proved to be effective in preventing herpes zoster virus in MM patients treated with bortezomib.[82] For ASCT recipients, prophylactic levofloxacin led to a 27% decrease in blood stream infection as well as a 31% decrease in fever and neutropenia.[83] However, the clinical significance of prophylactic antibiotic was limited due to increasing emergence of resistant strains, toxicity, drug interactions and suspected antagonistic effects. As such, antibiotics should only be prescribed on "high-infection-rate circumstances" such as induction therapy, progression or refractoriness.[84] What's more, previous data only suggest the validity of early prophylactic antibiotic use (about 2 months within the induction therapy) in MM patients.[85,86] Additionally, the efficacy of prophylactic gamma globulin for MM was not verified and the reduction of the number of malignant cells was cited as a most effective way of improving host defense.[87]

Infection and Tumor Progression

The scenario that many patients with MM have severe bacterial infections shortly before or after diagnosis [88–90] and the significant role of certain viruses in MM pathogenesis reveal a link between infection and tumor progression.[91,92] Pathogenic microorganisms expressing pathogen-associated molecular patterns can trigger toll-like receptors on MM cells, accelerate MM cell growth and prevent chemotherapy-induced apoptosis. [93–95] What's more, by promoting the secretion of immune agents, infections can accelerate tumor progression.[19,96,97] In this perspective, by promptly eradicating the pathogenic microorganisms and suppressing the pro-inflammatory immune milieu, antibiotics can theoretically represent both anti-tumor and anti-infection properties.

In fact, it was revealed *in vitro* in 2016 that the anti-infective chloramphenicol could induce MM cell apoptosis in a dose-relevant and time-dependent manner.[98] Simultaneously targeting two prominent intracellular protein degradation systems of the ubiquitin-proteasome system and the autophagy-lysosome system, macrolide antibiotics led to endoplasmic reticulum stress mediated and pro-apoptotic

transcription factor CADD153 induced apoptosis in MM cell lines.[99] Besides, thalidomide and clarithromycin were discovered to synergistically downregulate TNF-α and IL-6 secretion probably via ERK1/2 and AKT inhibition.[100] As previously mentioned, antibiotics and other anti-infectious agents (*i.e.,* vaccines, immunoglobulin, anti-viral drugs) have been successfully incorporated into MM regimens. Antibiotics suggest a synergistic action with other MM therapies. The combination of clarithromycin, low-dose thalidomide and dexamethasone (BLT-D) was of efficacy in patients with MM.[101] Another regimen of clarithromycin, lenalidomide, and dexamethasone (BiRD) also demonstrated effective in newly diagnosed MM.[102] Apart from antibiotics, for MM patients who underwent melphalan-based ASCT and developed ongoing parvovirus B19 infection, prophylactic intravenous immunoglobulin administration permitted prompt antineoplastic efficacy.[103]

Conclusions and Future Directions

Scientific progress is revolutionizing MM treatment, and development in immunotherapies as well as anti-infectious agents might thoroughly resolve the puzzle of immunodeficiency in near future. Promising immunotherapies involving mAbs, immune checkpoints inhibitors, therapeutic T-cells, vaccines/DC vaccines targeting specific immune mechanisms are currently under clinical and pre-clinical explorations. Rational combinations of immunotherapies, allo-SCT, chemotherapy, and antibiotics are ongoing to prolong progression-free survival with minimal toxicity. Further, some antibiotics such as clarithromycin and levofloxacin have been incorporated into MM treatment, and were of efficacy in prophylactic use.

Multiple myeloma is a most captivating example of "immune cancer", whereas in the authors' perspective, some immune signatures of MM still wait to be thoroughly described: (1) better targets in the mechanisms of immunodeficiency for MM diagnosis, prognosis, prophylaxis treatment and immunotherapies; (2) the precise correlation between peripheral immunity, microenvironment and tumor progression: is it adverse or favorable? Is it stage-related? What's the perfect timing for immunotherapies and antibiotics? (3) the distinct role of infection in different stages of MM and the clinical significance of prophylactic antibiotics.

Undoubtedly, combined therapies integrated with optimized modern clinical management will continue to deliver better anticipations for patients in years to come. With more biomarkers for pre-clinical and clinical myeloma to be defined, more emphasis will be laid on prophylaxis or early treatment and precision medicine. Hopefully, with collaborative efforts from oncologists, orthopedists, pathologists, pharmacologists, specialized nurses and the patients, the goal of MM treatment will eventually convert from "improving the length and quality of lives, achieving long-term disease-free survival", to ultimate cure of the disease.

Abbreviations

MM: Multiple myeloma; DC: dendritic cell; NK: natural killer; Tregs: T-regulatory cells; PD-1: programmed cell death protein-1; CTLA-4: cytotoxic T-lymphocyte associated protein 4; allo-SCT: allogeneic stem cell transplantation; mAbs: monoclonal antibodies; ADCC: antibody-dependent cellular cytotoxicity; CDC: complement-dependent cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; PD-L1: programmed cell death-ligand-1; PD-L2: programmed cell death-ligand-2; ASCT: autologous stem cell transplantation; TCRs: T-cell receptors; CARs: chimeric antigen receptors; CARTs: chimeric antigen receptor T cell therapies; HLA: human leucocyte antigen; GM-CSF: granulocyte macrophage colony-stimulating factor; BCMA: B cell maturation antigen; IMiDs: Immunomodulatory drugs.

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Competing Interests

The authors have declared that no competing interest exists.

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