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Review Article

Rapid Review on Multiple Myeloma; Current Clinical Management

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Abstract

Multiple myeloma (MM) is the second most common hematologic malignancy in adults, with 5-year relative survival in approximately 55.6% of patients. MM is a multifactorial disease in terms of diagnosis and treatment. The main challenge with the disease is that MM is characterized by multiple relapses and remissions with shorter remission intervals. Recently, cell therapy has improved remission in patients with relapsed or refractory MM. While avoiding vaccines that contain live viruses, COVID-19 vaccination is highly recommended for patients with MM. Here, we aim to rapidly review the literature and point out the current clinical management of MM.

Keywords: Multiple Myeloma; CAR T-Cell Therapy; Double-Hit Mm; Triple-Hit MM; COVID-19 Management

Diagnosis of multiple myeloma

Multiple myeloma (MM) is the second most common hematologic malignancy in adults over 45 years old and the 5-year relative survival in approximately 55.6% of patients [1,2]. MM is described by an overpopulation of malignant plasma cells in the bone marrow resulting in the accumulation of nonfunctional intact immunoglobulins or immunoglobulin chains [3]. MM begins with premalignant monoclonal gammopathy of undetermined significance (MGUS) and develops to smoldering myeloma. This malignancy leads to bone marrow failure followed by anemia, bone lesions, infections, hypercalcemia, renal failure, fatigue, and pain [4]. Table 1 summarizes the symptoms and clinical investigation for the diagnosis of MM.

The International Staging System (ISS) has defined three stages for MM related to albumin levels and the protein β_2-microglobulin. With the serum level of albumin above 35 g/L, the level of β_2-microglobulin above 3.5 mg/dL indicates stage 1. In stage 2 and stage 3 the level of β_2-microglobulin is between 3.5 - 5.5 mg/dL and over 5.5 mg/dL, respectively [3].

Diagnosis of Multiple Myeloma	
Symptoms	**Clinical Investigation**
Bone pain and pathological fractures	Skeletal survey X-rays may demonstrate lytic lesions and Osteopenia.
Anemia (bone marrow failure)	Full Blood Count; normochromic, normocytic anemia, Increased plasma cells (> 10%) in the bone marrow
Recurrent infections (due to immunoparesis)	Serum electrophoresis; reduced levels of normal immunoglobulins, Excess serum free light chains, either kappa or lambda, and monoclonal protein.
Hypercalcemia	Biochemistry; Raised calcium, with normal ALP
Renal failure	Renal stones, Increased susceptibility to UTI, Presence of lambda free light chains in urine, Elevated protein, Creatinine clearance
Hyperviscosity syndrome (ischemia, heart failure, and neurological problems)	Elevated Erythrocyte sedimentation rate (ESR) and Elevated Albumin, Creatinin, LDH, β_2-microglobulin in blood.

Table 1: Summary of diagnosis of MM [3,4].

Risk factor of multiple myeloma

A systematic review of meta-analyses demonstrated that MM is a multifactorial disease related to a combination of environmental,

lifestyle, and genetic factors [5]. Table 2 has summarized some of the possible factors that are associated with increased risk of MM. Briefly, exposure to some substances in the environment and poor lifestyle related to being overweight and obese may increase the risk of MM and mortality [5,6].

Moreover, chromosomal abnormalities and gene mutations can enhance myeloma cell growth and prevent apoptosis [5,7]. Regarding cytogenetic abnormalities listed in table 2, the presence of any two high-risk cytogenetic abnormalities is considered double-hit MM. Triple-hit MM refers to the presence of any three or more high-risk cytogenetic abnormalities [8].

MM Risk Factors				Ref
Environmental Factors	Pesticide exposure		DDT exposure, phenoxyacetics, and chlorophenols exposure	[10]
	metals exposure		Cadmium, antimony, lead	[11]
	chemical substances exposure Benzene Acrolein Polycyclic aromatic hydrocarbons Toluene Formaldehyde Trichlorophenol Xylene		Methylene chloride (dichloromethane)	[12]
			[11]	
	minerals exposure		Asbestos, crystalline, noncrystalline silica	[11]
Lifestyle Factors	Related to obesity adipocyte–bone marrow cell interactions modified Insulin Growth Factor-1		inflammatory cytokines [Tumor necrosis factor (TNF), Interleukin-1 (IL-1), Interleukin-6 (IL-6)]	[13]
			[14]	
			[15]	
Cytogenetic Factors	Chromosomal abnormalities and Gene mutation	Standard risk	Trisomies	[16]
			Gain 1q	
			t (11;14) (q13; q32) affected gene CCND1	
		High Risk	t (4;14) affected gene FGFR3 and MMSET	[9]
			t (14;16) affected gene C-MAF	
			t (14;20) affected gene MAF-B	
			17p13 deletions affected (p53)	[17]
			13q14 deletions (p53)	
	Other Gene mutations *C-myc* *NRAS* *KRAS*		methylation of the promotors of *P15INK4b* and *P16INK4a* genes	[7,8]
			[16]	

Table 2: Summary of factors associated with MM.

Current management of multiple myeloma

The newly diagnosed MM might be eligible for autologous stem cell transplantation (ASCT) based on the patient's age, performance status, and underlying condition or comorbidities. ASCT is not a curative approach, but it can advance median overall survival by approximately 12 months and can be delayed until relapse in selected patients with standard-risk MM [17]. First-line treatment for ASCT-eligible patients is a well-tolerated regimen consisting of Velcade

(bortezomib), lenalidomide, dexamethasone (VRd). The regimen of daratumumab, lenalidomide, and dexamethasone (DRd) is a suitable alternative for ASCT-ineligible patients or those intolerant to VRd [8]. The preferred regimen of bortezomib, cyclophosphamide, dexamethasone (VCd) is recommended for acute renal failure and nephropathy [18]. In high-risk patients, especially those with double-hit MM or triple-hit MM, the addition of daratumumab to the VRd regimen (Dara-VRd) is recommended [8]. Drug classification for management and treatment of MM are listed in table 3.

As MM is characterized by multiple relapses and remissions with shorter remission intervals, almost all patients with MM relapse after 3-4 years following initial diagnosis [20]. As shown in table 4, different triplet regimens are recommended for the first relapse in MM based on lenalidomide resistance. In the regimen for lenalidomide refractory MM, lenalidomide substitutes with another immunomodulatory drug, usually pomalidomide [21]. For the second and subsequent relapses, alkylating agents, proteasome inhibitors, and monoclonal antibodies must be added to the regimen.

Class	Name of drug
Alkylating agents	Melphalan, Cyclophosphamide
Corticosteroids	Dexamethasone, Prednisone
Anthracyclines	Doxorubicin and Liposomal Doxorubicin
Immunomodulatory drugs	Thalidomide, Lenalidomide, Pomalidomide
Proteasome inhibitors	Velcade (bortezomib), Carfilzomib, Ixazomib
Monoclonal antibodies	Daratumumab and Isatuximab (targeting CD38) Elotuzumab (SLAMF7 antigen)
Antibody-drug conjugate	Belantamab Mafodotin

Table 3: Drug classification for management and treatment of MM [9,20].

Recommendation for MM Treatment			Regimen
First-line	Standard Risk		Velcade (bortezomib), lenalidomide, and dexamethasone (VRd)
	High Risk		Daratumumab-VRd
Maintenance	Standard Risk		Lenalidomide,
	High Risk		Bortezomib
Relapse management	First relapse	Lenalidomide placid	Daratumumab, lenalidomide, dexamethasone (DRd). Carfilzomib, lenalidomide, dexamethasone (KRd). Ixazomib, lenalidomide, dexamethasone (IRd).
		Lenalidomide refractory	Carfilzomib, pomalidomide, dexamethasone (KPd). Daratumumab, bortezomib, dexamethasone (DVd). Bortezomib, pomalidomide, dexamethasone (DPd).
	Second or higher		Bortezomib, cyclophosphamide, dexamethasone (VCd). Selinexor, bortezomib, dexamethasone; Bendamustine-based regimens. Panobinostat added to proteasome inhibitor containing regimen. Venetoclax for t (11;14) myeloma; Anthracycline-containing regimen.

Table 4: Current management and treatment of MM [9,20].

New treatment approach for multiple myeloma

Over the last decade, the development of personalized immunotherapy for MM patients has been advanced by introducing the chimeric antigen receptor (CAR) T-cell therapies. CAR T-cell therapies can alter the patient's immune system to target tumor cells, resulting in overcoming drug resistance and inducing long-term remissions [22]. Besides, the production of pro-inflammatory cytokines leads to cancer cytolysis upon the interaction of CAR T-cells with MM cells. Therefore, CAR T-cells can destroy many tumor cells, and they may aid immune surveillance to prevent tumor recurrence [23,24]. The basic procedure of CAR T-cell therapies is demonstrated in figure 1.

B-cell maturation antigen (BCMA) refers to a protein expressed on the MM cells and other plasma cell malignancies [22,25]. Anti-BCMA CAR T-cell is the well-studied CAR T antigen target in MM and was approved as an orphan medicine under the name of Abecma for patients with relapsed or refractory MM [26-28].

Figure 1: The basic steps of CAR T-cell therapy for MM patients.

Recently, conditional marketing authorization of Abecma was granted based on results from a phase II clinical trial focusing on efficacy and safety of Abecma in 140 adult patients with relapsed or refractory MM [29]. Abecma demonstrated the overall response rate in 72 percent of patients, indicating complete or partial remission, while 28% of patients achieved a stringent complete response (sCR). For all responders, the median duration of response was 11 months, and for those who reached sCR, it was 19 months. An estimated 65 percent of sCR patients experienced at least a year of remission [29]. Abecma-related serious adverse reactions (SAR) and other side effects are listed in table 5.

Other than Abcema as anti-BCMA targeting MM, the clinical efficacy and safety of various other antigens are currently under investigation [23,28,31], and some of them are listed in table 6.

Serious adverse reactions (SAR)	Cytokine release syndrome (18%)
	General physical health deterioration (10%)
	Pneumonia (12%)
	Infections (19%)
	Viral infections (9%)
	Sepsis (7%)
	Febrile neutropenia (6%)
	Neurotoxicity (28%) neurotoxicity over Grade 3 (4%)
	Hemophagocytic lymph histiocytosis (HLH)/ macrophage activation syndrome (MAS) (4%)
	Fatal adverse reactions (6%)
Side effects	Fatigue, Musculoskeletal pain, Headache
	Upper respiratory tract infection, Cough
	Diarrhea, Nausea, Decreased appetite
	Hypogammaglobulinemia, Edema

Table 5: Abecma-related SAR and other side effects [31-33].

CAR name	Antigen	Reference
CTL019/tisagenlecleucel	CD19	[35,36]
CART-138	CD138	[37]
κ.CARTs	κ light chain	[38]
NA	SLAMF7	[24]
UCARTCS1	SLAMF7	[24]
NKG2D-CAR	NKG2D ligands	[39]
CAR2 Anti-CD38 A2	CD38	[24,40]
Combination of CD19 with various CDs in heme-malignancies	CD38 + CD19	[41]
NA	CD44v6 (+HSV-TK suicide gene)	[42]
NA	NY-ESO-1	[24]
LeY	Lewis Y	[43]

Table 6: Non-anti-BCMA CAR T-cell clinical trials in MM.

COVID-19 management in multiple myeloma

Impairment of the immune system by using immunosuppressive treatments with frequent use of corticosteroids increases the risk of infection, including COVID-19, in patients with MM [41]. It has been reported that mortality risk is higher in MM patients under daratumumab treatment or maintenance with lenalido-

mide-dexamethasone [42]. In MM patients, a severe inflammatory response compelled by COVID-19 resulted in acute hypogammaglobulinemia and increased mortality risk [43]. Therefore, preventative actions against infectious diseases, such as vaccination and self-care, are highly recommended for MM patients.

Recently, a clinical trial showed that the responses to mRNA vaccination against COVID-19 in patients with MM are associated with the stage and characteristic of MM [44]. Furthermore, this clinical trial also reported that mRNA-1273 (Moderna) vaccine had induced higher anti-spike antibody levels than BNT162b2 (Pfizer/BioNTech) in patients with MM [44]. Therefore, it is also recommended that other non-replicating adenoviral vector vaccines (e.g., Oxford/Astrazeneca, Janssen) and antigen/adjuvant vaccines (e.g., Novavax) should not pose any additional risk to MM patients [45].

Furthermore, in patients that had already been vaccinated against different infectious diseases, the course of MM treatment, specifically after allogeneic transplantation, leads to severe antibody titer reduction [41]. Therefore, recommendations for vaccinations of MM patients are like those made for the general population, patients with the impaired immune system, and patients treated with stem cell transplantation [46]. The recommended vaccines for all MM patients are Influenza, Pneumococci, Haemophilus influenza, and Herpes zoster [41]. However, the principle of avoiding live microorganisms (e.g., virus) vaccine applies to all recommended vaccines for MM patients. Vaccination against *Streptococcus pneumoniae* is highly recommended at the early diagnosis of MM before initiating any active therapy. The MM patients and their household members must be vaccinated against influenza annually [47].

Conclusion

This paper provided a quick overview of the literature focusing on the current clinical management of MM from diagnosis to treatment. Multiple factors that are associated with increased risk of MM are listed in this paper. Preventative actions may be recommended by improving lifestyle and avoiding environmental factors [5,6]. Clinical treatment of MM is started with a first-line regimen followed by a maintenance regimen and relapse management [8,19]. Eventually, the drug-resistant will happen through multiple relapses with shorter remission intervals in MM patients [21]. However, the recently approved CAR T-cell therapy (Abcema) extends the remission and improves survival in patients with relapsed or refractory MM [29]. Thus, for MM patients, CAR T-cell therapies have offered a new therapeutic development approach towards personalized treatment. Regarding the COVID-19 vaccination, the Moderna vaccine has induced a better immune response [44]. However, vaccination against COVID-19 by any available approved vaccine, excluding those containing the live virus, is recommended for MM patients and their household/caregivers [45]. However, more studies are required to advise the number of doses and intervals between doses for MM patients.

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