REVIEW

Cellular Immunotherapies for Multiple Myeloma: Current Status, Challenges, and Future Directions

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ABSTRACT

Multiple myeloma (MM) remains incurable due to relapse, although the use of proteasome inhibitors, immunomodulatory drugs, CD38-targeting antibodies, and autologous stem cell transplantation (auto-SCT) significantly improve the clinical outcomes of patients with newly diagnosed MM. In recent years, the introduction of chimeric antigen receptor T-cell (CAR T-cell) therapy has brought hope to patients with refractory and relapsed MM. The graft-versus-myeloma effect of allogeneic SCT provides the possibility for curing a subset of MM patients. In this review, we summarize the recent advances and challenges of cellular immunotherapies for MM, focusing on auto-SCT, allogeneic SCT, and CAR T-cell approaches. We also discuss future directions, and propose a specific algorithm for cellular therapies for MM and probability of minimal residual disease-directed therapy.

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Key Summary Points

Autologous stem cell transplantation (auto-SCT) remains the standard of care for transplant-eligible patients with newly diagnosed multiple myeloma.

Chimeric antigen receptor T-cell (CAR T-cell) therapy has been successfully used for the treatment of refractory/relapsed (R/R) Multiple myeloma (MM). The preliminary results of CAR T-cell bridging to SCT for patients with R/R MM are promising.

Long-term follow-up suggests that allogeneic SCT can provide an opportunity for curing a subset of MM patients.

In the era of new targeted therapies, minimal residual disease-directed treatment or intervention represents an important step for realizing precision medicine in patients with MM.

INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy, responsible for 98,437 deaths globally in 2016 [1–5]. At present, patients with MM cannot be cured [2, 3, 5, 6], although the clinical use of immunomodulatory drugs (IMiD), proteasome inhibitors, cluster of differentiation 38 (CD38)-targeting antibodies, and autologous stem cell transplantation (auto-SCT) has significantly extended survival time [1, 7–13]. In recent years, the introduction of chimeric antigen receptor T-cell (CAR T-cell) therapy has improved the prognosis of refractory and relapsing MM (R/R-MM) [6, 14–25]. Moreover, long-term follow-up has offered preliminary evidence that the existence of the graft-versus-myeloma effect after allogeneic SCT (allo-SCT) can improve outcomes and provide the

possibility for curing a subset of patients with newly diagnosed MM (NDMM) [26–34]. Herein, we discuss the recent advances and challenges of cellular immunotherapies for MM, focusing mainly on auto-SCT, allo-SCT, and CAR T-cell approaches (Tables 1, 2, and 3). We provide an outlook on future prospects and challenges in cellular therapy and note that dealing with relapse [35], minimal residual disease (MRD)-directed therapy [7, 36–39], and combinations of different cellular therapy methods are active research areas in terms of improving prognosis for MM patients. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CURRENT STATUS

Auto-SCT

Auto-SCT for Patients with NDMM
In the era of targeted therapies such as BCMA-CD3 bispecific antibody, CAR natural killer (NK) cells, belantamab mafodotin, and venetoclax, auto-SCT remains the standard of care for transplant-eligible (TE) patients with NDMM (Table 1) [4, 5, 9, 10, 12, 13, 40–62].

Induction Therapy Current guidelines [2–4] recommend triplet regimens as induction therapy (IT) for TE patients with the addition of an IMiD, such as bortezomib, lenalidomide, and dexamethasone (VRD), bortezomib, thalidomide, and dexamethasone (VTD), and carfilzomib, lenalidomide, and dexamethasone (KRD), which are preferred to cyclophosphamide-containing regimens such as bortezomib, cyclophosphamide, and dexamethasone (VCD), and carfilzomib, cyclophosphamide, and dexamethasone (KCD).

In a recent study, 270 TE patients with NDMM were randomized 1:1 to daratumumab (DARA) plus RVD (D-RVD) and RVD groups [45]. The authors observed a higher stringent complete response (sCR) rate for cases in the D-RVD group than that for cases in the RVD group (42.4% vs. 32.0%; one-sided $P = 0.068$) by the end of post-auto-SCT consolidation. After a

Table 1 Recent studies on the outcomes of MM patients who received autologous stem cell transplantation

Author, year, Ref	No. Pts.	Age (M)	Diagnosis	Treatment modality	Maintenance after transplant	PFS
Gay et al. 2021 [60]	158	57	NDMM	KRD + auto-SCT	KR or R alone	4 years 69%
	157	57	NDMM	KRD12	KR or R alone	4 years 56%
	159	57	NDMM	KCD + auto-SCT	KR or R alone	4 years 51%
Moreau et al. 2021 [12]	543	59	NDMM	D-VTD + auto-SCT	DARA or obser	1.5 years 93%
	542	58	NDMM	VTD + auto-SCT	DARA or obser	1.5 years 85%
Jackson et al. 2021 [53]	1021	61	NDMM	CRD + auto-SCT	R or R and vorinostat or obser	36.00 months
	1021	61	NDMM	CTD + auto-SCT	R or R and vorinostat or obser	33.00 months
Usmani et al. 2021 [10]	52	66	HR-NDMM	RVD + auto-SCT	RVD	33.64 months
	48	62	HR-NDMM	RVD-elotuzumab + auto-SCT	RVD + elotuzumab	31.47 months
Goldschmidt et al. 2021 [61]	139	61.3	R-MM	RD + auto-SCT	R	20.70 months
	138	61.2	R-MM	RD	RD	18.80 months
Mai et al. 2021 [55]	353	≤ 60 (S1)	NDMM	Tandem auto-SCT	R	N/A
	107	61–65 (S2)	NDMM	Tandem auto-SCT	R	HR 1.28; $P = 0.11$
	141	66–70 (S3)	NDMM	Tandem auto-SCT	R	HR 1.00; $P = 0.99$
Baertsch et al. 2021 [46]	138	56	NDMM	BTZ-based triplet IT + auto-SCT	BTZ	N/A
	183	57	NDMM	BTZ-based triplet IT + auto-SCT	R	HR 0.83; $P = 0.18$
Gregersen et al. 2021 [51]	82	60	R-MM	KCD + auto-SCT	KD	25.10 months
	86	62	R-MM	KCD + auto-SCT	Placebo	16.70 months
Jackson et al. 2021 [52, 53]	526	61	NDMM	KRDc	R or obser	3 years 81.8%
	530	62	NDMM	RDc/TDc	R or obser	3 years 75.1%

Table 1 continued

Author, year, Ref	No. Pts.	Age (M)	Diagnosis	Treatment modality	Maintenance after transplant	PFS
Voorhees et al. 2020 [45]	104	59	NDMM	D-RVD + auto-SCT	R or R and DARA	2 years 95.8%
	103	61	NDMM	RVD + auto-SCT	R or R and DARA	2 years 89.8%
Tacchetti et al. 2020 [9]	241	56.3	NDMM	VTD + auto-SCT	DEX	10 years 34%
	239	55.9	NDMM	TD + auto-SCT	DEX	10 years 17%
Dimopoulos et al. 2019 [66]	395	58	NDMM	Auto-SCT	Ixazomib	26.50 months
	261	60	NDMM	Auto-SCT	Placebo	21.30 months

MM multiple myeloma, *Ref* reference, *Pts.* patients, *No.* number, *M* median, *PFS* progression-free survival, *NDMM* newly diagnosed MM, *R-MM* relapsed MM, *KRD* carfilzomib, lenalidomide, dexamethasone, *KR* carfilzomib, lenalidomide, *R* lenalidomide, *auto-SCT* autologous stem cell transplantation, *KCD* carfilzomib, cyclophosphamide, dexamethasone, *D-VTD* daratumumab, bortezomib, thalidomide, dexamethasone, *DARA* daratumumab, *CRD* cyclophosphamide, lenalidomide, dexamethasone, *CTD* cyclophosphamide, thalidomide, dexamethasone, *HR-NDMM* high-risk NDMM, *RVD* (*VRD*) bortezomib, lenalidomide, dexamethasone, *RD* lenalidomide, dexamethasone, *BTZ* bortezomib, *IT* induction therapy, *obser* observation, *KD* carfilzomib, dexamethasone, *KRDc* carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide, *RDc* lenalidomide, dexamethasone, and cyclophosphamide, *TDc* thalidomide, dexamethasone, and cyclophosphamide, *DEX* dexamethasone

median follow-up of 22.1 months, the sCR rates (62.6% vs. 45.4%; $P = 0.0177$) and MRD negativity (10^{-5} threshold) rates (51.0% vs. 20.4%; $P < 0.0001$) were further improved. Recent updated data showed that the estimated 36-month progression-free survival (PFS) rate was 88.9% and 81.2% for the D-RVD group and RVD group, respectively. Subgroup analysis showed the superiority of DARA and lenalidomide over placebo for maintenance. These results support the use of D-RVD, DARA, and lenalidomide in TE NDMM patients.

In the randomized, open-label, phase 3 CASSIOPEIA trial, Moreau et al. [63] first demonstrated the clinical benefit of DARA plus standard of care in TE patients with NDMM, including a better sCR rate (D-VTD 29% vs. VTD 20%, $P = 0.0010$), a better MRD negativity rate (D-VTD 64% vs. VTD 44%, $P < 0.0001$), and a longer median PFS from the first randomization (hazard ratio 0.47, $P < 0.0001$). Roussel et al. [8] further reported the clinical benefits observed with D-VTD versus VTD, both of which

supported the addition of DARA to standard regimens in patients with NDMM. The benefits of adding DARA to RD led to increased overall survival (OS) and PFS in patients with NDMM ineligible for auto-SCT [11]. In a phase III trial, Goldschmidt et al. [64] for the first time observed that, compared with RVd, RVd with the anti-CD38 monoclonal antibody (CD38-moAb) isatuximab was associated with higher MRD negativity after IT in TE patients with NDMM.

Overall, for TE patients with NDMM, the aim of IT was to achieve maximal response with four to six cycles of therapy before auto-SCT. The European Medicines Agency has approved D-VTD as a new standard of care for IT pre-auto-SCT for patients with TE NDMM [2–4]. Therefore, in the near future, quadruplet regimens such as D-RVD and isatuximab + VRD might be accepted as novel standard approaches.

Conditioning Regimen In a recent study by Bashir et al. [65], 205 patients were randomly

Table 2 Recent studies on the outcomes of MM patients who received CAR T-cell therapy

Author, year, Ref	No. Pts.	Age (M)	Diagnosis	Phase	Target antigen	CD	LD	CAR T dose	CRS (overall)	OR	CR	MRDneg	PFS
Yan et al. 2021 [15]	10	57	R/R MM	N/A	BCMA, CD19	4-1BB	FC	3.0–$6.5 \times 10^7/kg$		90%%	57%%	90%	24 months
Munshi et al. 2021 [16]	128	61	R/R MM	II	BCMA	4-1BB	FC	150×10^6 to 450×10^6 CAR-positive (CAR+) T cells	84%	73%	33%	26%	8.8 months
Berdeja et al. 2021 [17]	97	61	R/R MM	Ib/II	BCMA	4-1BB	FC	0.75×10^6 CAR-positive viable T cells/kg	95%	97%	67%	93% (53/57)	1 year 77%
Zhang et al. 2021 [18]	61	59	R/R MM	N/A	BCMA	4-1BB	FC	$1.1 \times 10^6/kg$ to $6.2 \times 10^6/kg$	98.40%	98.30%	70.30%	N/A	1 year 50.2%
Mei et al. 2021 [19]	23	59	R/R MM	I	BCMA, CD38	4-1BB	FC	0.5, 1.0, 2.0, 3.0, and 4.0×10^6 CAR T cells/kg	87%	86%	52%	87%	17.2 months
Deng et al. 2021 [20]	20	58	R/R MM	N/A	BCMA	4-1BB	FC	2×10^6 cells/kg	80%	9/20	N/A	1 year 72.5%	1 year 81%
Wang et al. 2020 [6]	18	53.5	R/R MM	I	BCMA	4-1BB	FC	1, 3, and 6×10^6 CAR-positive T cells/kg	70.60%	100%	72.20%	94% (17/18)	1 year 58.3%
Raje et al. 2019 [21]	33	60	R/R MM	I	BCMA	4-1BB	FC	50×10^6, 150×10^6, 450×10^6, or 800×10^6	76%	85%	45%	94% (15/16)	11.8 months

Table 2 continued

Author, year, Ref	No. Pts.	Age (M)	Diagnosis	Phase	Target antigen	CD	LD	CAR T dose	CRS (overall)	OR	CR	MRDneg	PFS
Yan et al. 2019 [22]	21	58	R/R MM	II	BCMA, CD19	4-1BB	FC	1×10^6 cells/kg	90%	95%	43%	N/A	16.2 moths
Xu et al. 2019 [23]	17	56	R/R MM	I	BCMA	4-1BB	FC or Cy alone	0.7×10^6 cells/kg	100%	15/17	13/21	N/A	1 year 52.9%
Brudno et al. 2018 [24]	24	N/A	R/R MM	N/A	BCMA	CD28	FC	0.3 to 3×10^6 CAR+ T cells/kg	100%	81%	61%	50%	N/A
Zhao, et al. 2018 [25]	57	55	R/R MM	I	BCMA	4-1BB	Cy	0.07 to 2.1×10^6	90%	88%	68%	63%	15.00

MM multiple myeloma, *CAR T cell* chimeric antigen receptor T cell, *Ref* reference, *Pts.* patients, *No.* number, *M* median, *CD* costimulatory domain, *LD* lymphodepletion, *CRS* cytokine release syndrome, *OR* overall response, *CR* complete response, *MRDneg* negative minimal residual disease, *PFS* progression-free survival, *N/A* not available, *R/R MM* refractory or relapsed MM, *BCMA* B-cell maturation antigen, *CD19* cluster of differentiation 19, *CD38* cluster of differentiation 38, *CD28* cluster of differentiation 28, *FC* fludarabine and cyclophosphamide, *Cy* cyclophosphamide

Table 3 Recent studies on the outcomes of MM patients who received allogeneic stem cell transplantation

Author, year, Ref	No. Pts.	Age (M)	Diagnosis	Transplant modality	II–IV aGVHD	cGVHD	Relapse	TRM	PFS	OS	GRFS
Luoma et al. 2021 [26]	205	51.7	NDMM + R-MM	Allo-SCT	24%	5 yrs 62%	10 yrs 68%	10 yrs 12%	10 yrs 20%	10 yrs 43%	N/A
Sahebi et al. 2021 [27]	295	55	R-MM	Allo-SCT	30%	2 yrs 27%	2 yrs 54%	2 yrs 19%	2 yrs 26%	1 yrs 58%	2 yrs 24%
Gagelmann et al. 2021 [28]	446	N/A	NDMM	Auto-SCT	N/A	N/A	5 yrs 1%	5 yrs 82%	5 yrs 17%	5 yrs 51%	N/A
	105	N/A	NDMM	Tandem auto-SCT	N/A	N/A	5 yrs 4%	5 yrs 63%	5 yrs 33%	5 yrs 60%	N/A
	72	N/A	NDMM	Auto/allo-SCT	N/A	N/A	5 yrs 10%	5 yrs 56%	5 yrs 34%	5 yrs 67%	N/A
Hayden et al. 2021 [29]	156	60	R-MM (74%)	Secondary allo-SCT	27%	2 yrs 36%	5 yrs 79%	5 yrs 15%	5 yrs 6%	5 yrs 25%	N/A
Costa et al. 2020 [30]	899	56	NDMM	Tandem auto-SCT	N/A	N/A	10 yr 77.2%	10 yrs 8.3%	10 yrs 14.4%	10 yrs 36.4%	N/A
	439	53	NDMM	Auto/allo-SCT	N/A	N/A	10 yrs 61.6%	10 yrs 19.7%	10 yrs 18.7%	10 yrs 44.1%	N/A
Holstein et al. 2020 [31]	57	50	NDMM	Auto-SCT/RIC-allo-SCT	27%	57%	N/A	2%	3.6 yrs (median)	6.6 yrs (median)	N/A
Knop et al. 2019 [32]	126	52	NDMM	Tandem auto-SCT	N/A	N/A	N/A	2 yrs 4.1%	2 yrs 46.8%	71.8	N/A
	73	56	NDMM	Auto/allo-SCT	28%	32.80%	N/A	2 yrs 14.3%	2 yrs 59%	70.2	N/A

Table 3 continued

Author, year, Ref	No. Pts.	Age (M)	Diagnosis	Transplant modality	II–IV aGVHD	cGVHD	Relapse	TRM	PFS	OS	GRFS
Sahebi et al. 2019 [33]	96	54.9	R-MM	Haplo-SCT	39%	2 yrs 46%	2 yrs 56%	2 yrs 26%	2 yrs 17%	2 yrs 48%	N/A
Greil et al. 2019 [34]	109	56	NDMM	Allo-SCT	25%	24%[a]	10 yrs 67.6%	10 yrs 12.4%	10 yrs 20.1%	10 yrs 26.1%	N/A

MM multiple myeloma, *yrs* years, *Ref* reference, *Pts.* patients, *No.* number, *M* median, *aGVHD* acute graft-versus-host disease, *cGVHD* chronic GVHD, *TRM* transplant-related mortality, *PFS* progression-free survival, *OS* overall survival, *GRFS* GVHD- and relapse-free survival, *NDMM* newly diagnosed MM, *R-MM* relapsed MM, *allo-SCT* allogeneic stem cell transplantation, *RIC* reduced-intensity conditioning, *haplo-SCT* haploidentical SCT, *auto-SCT* autologous SCT, *N/A* not available

[a] Indicates moderate to severe chronic GVHD

assigned to a group receiving melphalan alone (MEL group, $n = 98$) and those receiving busulfan plus melphalan (BU/MEL group, $n = 104$). The authors reported a median PFS of 43.5 months and 64.7 months for the MEL and BU/MEL groups, respectively. Although several researchers have demonstrated favorable survival outcomes with BU/MEL and carmustine/MEL conditioning compared with those of high-dose MEL (HDM), HDM (200 mg/m^2) has remained the recommended conditioning regimen for TE patients with NDMM [2–4, 41]. In our opinion, new multicenter randomized studies are needed to elucidate whether BU/MEL and carmustine/MEL could become a new standard of care in the future.

Consolidation and Maintenance Therapy Consolidation or maintenance therapy can maximize the benefit of auto-SCT by prolonging PFS from the initial diagnosis [12, 43, 45]. The approaches for consolidation include bortezomib alone or plus other agents such as VTD and VRD, and for maintenance include lenalidomide [44, 52], bortezomib (especially for patients with high-risk cytogenetics), and ixazomib. However, thalidomide was not recommended [2–4, 41].

Recent advances in consolidation and maintenance therapy have mainly focused on DARA and ixazomib. Voorhees et al. [45] showed that the depth of response in patients with TE NDMM could be improved by D-RVD consolidation, with no new safety concerns. Moreau et al. [12] found that the risk of disease progression or death was significantly reduced after DARA maintenance every 8 weeks for 2 years compared with observation only. Data obtained from the oral ixazomib maintenance following autologous stem cell transplantation-MM3 study demonstrate a significantly higher rate of deepening responses with ixazomib versus placebo maintenance as well as a correlation of deepening response with prolonged PFS [43]. Therefore, DARA or ixazomib maintenance could prolong PFS and represent a new option for maintenance therapy after auto-SCT in patients with NDMM [66].
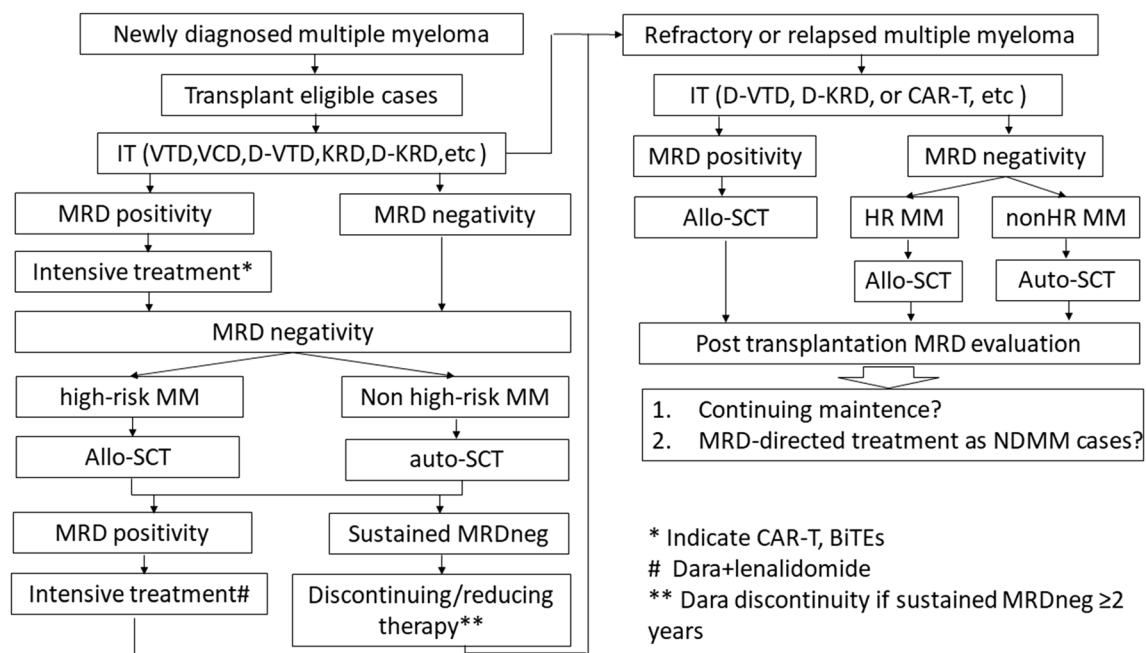
Fig. 1 Proposed algorithm for cellular therapies to treat MM and probability of MRD-directed therapy. *MM* multiple myeloma, *MRD* minimal residual disease, *IT* induction therapy, *KRD* carfilzomib, lenalidomide, dexamethasone, *VTD* bortezomib, thalidomide, and dexamethasone, *VCD* bortezomib, cyclophosphamide, and dexamethasone, *D-VTD* daratumumab plus VTD, *KRD* carfilzomib, lenalidomide, and dexamethasone, *D-KRD* daratumumab plus KRD, allo-*SCT* allogeneic stem cell transplantation, *auto-SCT* autologous stem cell transplantation, *MRDneg* negative MRD, *NDMM* newly diagnosed MM, *HR-MM* high-risk MM, *BiTEs* bispecific T-cell engagers, *Dara* daratumumab. ‡Indicates that patients with standard-risk MM at diagnosis should not be treated according to MRD status

Salvage Auto-SCT

According to the current literature [2–4, 41], salvage auto-SCT is recommended for patients whose disease was controlled by the first auto-SCT for 18 months or longer. In addition, salvage or delayed auto-SCT could also be used as consolidation in first relapse for those choosing not to proceed to auto-SCT initially. For patients with DARA-refractory MM, one study reported median PFS and OS of 7.2 and 19.3 months, respectively, for an entire patient cohort receiving salvage auto-SCT [67]. The authors showed that factors including younger age, better performance status, low-risk GEP70 gene expression profile, and longer time interval from initial MM diagnosis/initial auto-SCT to salvage auto-SCT were associated with improved survival. In the era of novel agent therapy, the benefit of salvage auto-SCT was further confirmed in the German randomized myeloma multicenter group phase III ReLApsE trial [61].

More recently, data from the Center for International Blood and Marrow Transplant Research registry suggested that patients who received maintenance regimens, including lenalidomide (42%), pomalidomide (13%), and bortezomib (13%), after salvage auto-SCT showed superior outcomes, including non-relapse mortality (NRM; 2% vs. 9.9%, $P < 0.01$), relapse (70.2% vs. 80.3%, $P < 0.01$), PFS (27.8% vs. 9.8%, $P < 0.01$), and OS (54% vs. 30.9%, $P < 0.01$), at 5 years compared to the no-maintenance group [56]. Available data supported the notion that maintenance was also recommended for patients receiving salvage auto-SCT [2–4, 41].

In summary, auto-SCT remains an important part of therapy for patients with NDMM and relapsing MM (Table 1). The available novel
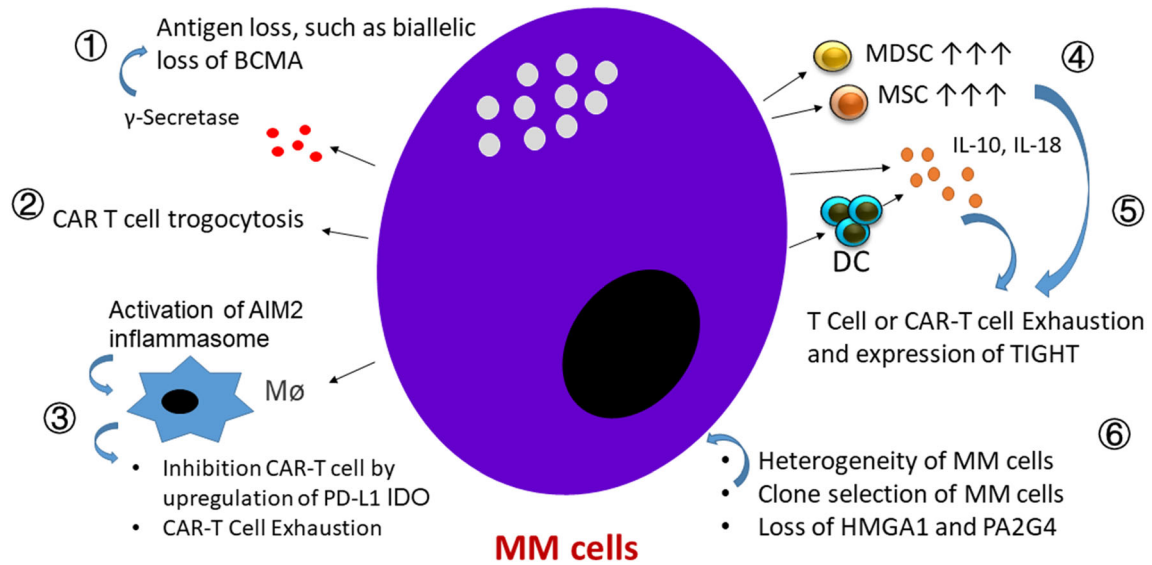
Fig. 2 Underlying mechanisms of CAR T-cell therapy resistance or relapse after transplantation. ① BCMA could be actively cleaved from the tumor cell surface by the ubiquitous multi-subunit γ-secretase complex; ② reversible antigen loss could be provoked by CAR T-cell trogocytosis; ③ inhibition of CAR T-cell function by macrophages; ④ MDSC and MSC as well as ⑤ IL-10 and IL-18 in bone marrow microenvironment could induce T-cell or CAR T-cell exhaustion; ⑥ loss of HMGA and PA2G4 could promote proliferation, migration, and adhesion abilities of MM cells. *CAR T-cell* chimeric antigen receptor T cell, *Mø* macrophage, *MDSC* myeloid-derived suppressor cells, *MSC* mesenchymal stem cells, *DC* dendritic cells, *IL-10* interleukin-10

agents have been incorporated into induction, conditioning, consolidation, and maintenance regimens in relation to auto-SCT, which offered both PFS and OS benefits, even in patients with high-risk disease [38, 45, 60, 68–70]. The role, timing, and outcomes of auto-SCT will continue to be updated and improved as next-generation novel therapies continue to be developed and as our ability to detect MRD continues to improve.

CAR T-Cell Therapy

CAR T-cell therapy has achieved significant success in the treatment of R/R MM both in China and in other countries of the world (Table 2) [6, 14–25, 71–73]. At present, at least 600 patients with R/R MM who received CAR T-cell therapy have been reported [6, 14–25, 71–73]. The targeted antigens included B-cell maturation antigen (BCMA), CD38, and CD19, although preclinical and clinical trials on other antigens such as CD138, CD56, signaling lymphocyte activation molecule F7 (SLAMF7), natural killer group 2 member D (NKG2D) [74], and orphan G protein-coupled receptor class C group 5 member D (GPRC5D) were ongoing. A fludarabine and cyclophosphamide regimen was routinely used for lymphodepletion in nearly all publications. The overall response (OR) and CR rates after CAR T-cell therapy ranged from 73% to 100% and from 33% to 72%, respectively. The cytokine release syndrome (CRS) rate ranged from 71% to 100%, and 1-year PFS ranged from 50% to 77%. Overall, current CAR T-cell therapy for patients with R/R MM showed a remarkably high OR rate, but durable response has not yet been observed [6, 14–25, 71–73]. Therefore, some questions still remain in this field: first, the specific mechanisms underlying relapse and immune escape; second, how to decrease the incidence of CAR T-cell toxicity and determine the best treatment; and third, how to deal with the issue on CAR T-cell access and cost. Apart from CAR T-cell therapy for BCMA, both belantamab mafodotin, an immunoconjugate targeting BCMA, and bispecific T-cell engager, a

BiTE® molecule binding BCMA on MM cells and CD3 on T cells, represent novel strategies for R/R MM [75, 76].

Allo-SCT

Allo-SCT remains a curative treatment for patients with hematological disease, particularly in the era where everyone has a transplant donor because of the wide application of haploidentical allograft [77, 78]. Progress has been made in recent years (Table 3) [26–34, 58, 79–85]; although allo-SCT for MM has not been routinely recommended, it might be considered in select high-risk patients or in the context of a clinical trial [2–4]. In a phase 3 trial, Knop et al. [32] compared the outcomes of patients with NDMM with del(13q)who received either tandem auto-SCT ($n = 199$) or auto-SCT followed by reduced-intensity conditioning allo-SCT (auto-/allo-SCT, $n = 126$). After a median follow-up of 91 months, patients in the auto-/allo-SCT group experienced longer PFS (34.5 vs. 21.8 months, $P = 0.003$) but higher 2-year NRM (14.3% vs. 4.1%, $P = 0.008$) compared to those in the auto-SCT group. Subgroup analysis showed that treating patients harboring both del(13q) and del(17p) with auto-/allo-SCT ($n = 19$) achieved longer median PFS (37.5 vs. 6.1 months, $P = 0.0002$) and OS (61.5 vs. 23.4 months, $P = 0.032$) compared to treatment with tandem auto-SCT ($n = 6$). These findings suggested that auto-/allo-SCT significantly extended PFS versus tandem auto-SCT in del(13q) MM, and indicate some survival benefit for first-line allo-SCT in high-risk MM.

More recently, Costa et al. [30] performed a pooled analysis to compare the outcomes between tandem auto-SCT ($n = 899$) and auto-/allo-SCT ($n = 439$) after IT based on individual patient data from four clinical trials. After a median follow-up of 118.5 months for survivors, the authors observed that patients who underwent auto-/allo-SCT had lower 10-year NRM (8.3% vs. 19.7%, $P < 0.001$) and risk of relapse (61.6% vs. 77.2%, $P < 0.001$) and better PFS (HR 0.84, $P = 0.004$) and OS (HR 0.84, $P = 0.02$). This study suggested that the existence of graft-versus-myeloma after allograft

could improve outcomes and cure a subset of patients.

Currently, the choice of indications for allo-SCT in patients with high-risk MM or R/R MM is fairly significant [26–28, 32, 34, 79]. It was expected that the discovery of new biomarkers that could be used to identify patients who would benefit from allograft would lead to a greater number of cases that would be cured, not just those cases with high-risk MM, such as del(17p) patients and those who experienced early relapse after drug treatment with or without auto-SCT (Fig. 1).

CHALLENGES WITH CELLULAR IMMUNOTHERAPIES

How to Cope with Relapse After Auto-SCT or CAR T-Cell Resistance

Understanding the mechanisms of relapse after either transplantation or CAR T-cell therapy might provide novel insight into the prevention of recurrence [35, 86–90]. Available reports in the literature suggest several mechanisms [22, 88, 91, 92]: First, CARs could provoke reversible antigen loss through trogocytosis, which leads to decreased target density on tumor cells and abated T-cell activity by promoting fratricide T-cell killing and T-cell exhaustion [93]. Second, CAR T-cell therapy could induce the phenotype switch of the macrophages by upregulating the expression of programmed death ligand 1 and indoleamine 2,3-dioxygenase, consequently inhibiting the cytotoxicity of CAR T cells and proliferation of activated T cells [94]. Other mechanisms for CAR T resistance included CAR T-cell exhaustion, release of interleukin-10 (IL-10) and IL-18 by MM cells, and clone selection of MM cells (Fig. 2). Strategies for CAR T-cell therapy resistance included the following [89, 90, 95, 96]: (i) cooperative killing and combinatorial targeting to augment tumor responses to immunotherapy; (ii) enhanced antitumor effects of CAR-T therapy by combination with blockade of the AIM2 inflammasome and α1-AR; (iii) simultaneous application of anti-BCMA CAR-T with lenalidomide; (iv) treating R/R MM

patients with CAR-T-cell plus immune check-points inhibitors; (vi) novel CAR-T design [89, 90, 96, 97], including SLAMF7 CAR T cells, CD126 CAR T cells, dual-specific, trimeric APRIL-based CAR T cells [98], and CD229-specific CAR T cells, as well as the engineering of BCMA/CS1 OR-gate CAR T-cells; (vii) the possibility that CAR natural killer cells might be less toxic and present better anti-MM effects [74].

Could MRD-Directed Therapy be Successfully Used for MM Patients?

Currently, MRD has been routinely used for response evaluation and prediction of disease progression in patients with MM [7, 36–39]. Recent advances provided promising results showed that MRD-directed therapy could further improve the survival of patients with MM. For example, in a multicenter, multinational, retrospective study enrolling 400 patients with MRD monitoring during front-line therapy, Martinez-Lopez et al. [99] reported median PFS of 104 and 45 months for patients achieving MRD negativity at any point and those with persistent MRD positivity, respectively ($P < 0.0001$). The authors also observed that a treatment change based on MRD significantly prolonged PFS in comparison with cases in which MRD results were not acted upon (mPFS 104 vs. 62 months, $P = 0.005$). During maintenance, stopping therapy in patients with MRD negativity on at least one occasion did not alter PFS. Impressively, intensification or change of therapy for patients with a positive MRD ($n = 43$) resulted in better PFS compared to those in whom no adjustment was made ($n = 171$) (mPFS NA vs. 39 months, $P = 0.02$). These data suggest that MRD is useful in guiding clinical decisions during initial therapy and has a positive impact on PFS in MM patients, similar to MRD-directed therapy in patients with acute leukemia [100].

Although the available preliminary data remain to be confirmed in prospective randomized clinical trials, these studies have opened a new dimension for the use of MRD in MM [100–103]. Therefore, we propose an algorithm for MRD-directed therapy of patients with MM, which might be helpful for outcome improvement (Fig. 1).

How Cellular Immunotherapies Should be Combined with Other Methods for MM

Over the past few years, a number of novel methods have been developed, such as CC-93269, a bispecific antibody that recognizes both BCMA and CD3ε, allogeneic CAR T cells [104]. More recently, an open-label, single-arm, phase 1 study enrolled patients ($n = 157$) with MM who were relapsed, refractory, or intolerant to established therapies. Teclistamab (a bispecific antibody that binds BCMA and CD3 to redirect T cells to MM cells) was administered with step-up dosing for 38.4 μg/kg or higher doses. Among response-evaluable patients treated at the recommended phase 2 dose ($n = 40$), the OR was 65%, and 58% achieved a very good partial response or better [105]. These data suggest that teclistamab is a novel treatment approach for R/R MM with durable responses and is well tolerated.

With regard to the combination of CAR T-cell therapy and allo-SCT, Qian et al. [73] presented the case of a heavily pretreated young patient with relapsed extramedullary MM (EMM) and refractoriness to bortezomib, ixazomib, lenalidomide, auto-SCT, and DARA, and indicated that myeloablative haploidentical-SCT as salvage treatment for relapse after CAR T-cell therapy targeting BCMA was feasible. The feasibility of combining CAR T cells with auto-SCT for MM has also been reported by other researchers [106, 107].

Considering the contemporary literature collectively [73, 106, 107], the promising results regarding the effects of anti-BCMA CAR T-cell therapy and allo-SCT may provide a proof of principle for patients with EMM [73]. Therefore, for patients with MM, particular R/R MM, prospective multicenter studies are needed to address the potential for combining CAR-T-cell therapy, auto-SCT, or allo-SCT with novel methods to improve outcomes.

Key Points
- Auto-SCT remains the standard of care for TE patients with NDMM. The application of novel targeted therapies, such as DARA and ixazomib, in IT and consolidation as well as maintenance therapy further improves transplant outcomes.
- CAR T-cell therapy has been successfully used for the treatment of R/R MM. The preliminary results of CAR T-cell bridging to SCT for patients with R/R MM are promising.
- Long-term follow-up suggests that allo-SCT can provide an opportunity for curing a subset of MM patients.
- In the era of new targeted therapies, MRD-directed treatment or intervention represents an important step for realizing precision medicine in patients with MM.

Questions Remaining to be Answered
- The best regimen for induction therapy or consolidation therapy or maintenance
- The best conditioning regimen for auto-SCT
- The indications for allo-SCT in patients with NDMM or R/R MM
- How to define the cases that will be cured by allo-SCT
- How to further elucidate the underlying mechanisms of CAR T-cell therapy resistance or relapse after transplantation
- How to enhance the anti-myeloma activity of CAR T-cell therapy
- Whether multicenter prospective studies are needed to confirm the feasibility and efficiency of CAR T-cell therapy bridging to SCT for patients with R/R MM
- Whether haploidentical allograft can be successfully used for MM treatment
- Whether prospective, randomized studies are needed to confirm MRD-directed therapy in the field of MM
- Other issues, such as how to find novel targets for treatment of MM.

FUTURE DIRECTIONS

Recent advances in cellular immunotherapies [14–25] such as auto-SCT, allo-SCT, and CAR T-cell therapy [26–34] have to a certain extent changed their position in MM treatment as well as the landscape of MM, especially R/R MM. In the future, we will see the following advances. First, the combination of auto-SCT, allo-SCT, and CAR T-cell therapy as well as the combination of these approaches with other methods, including DARA and ixazomib, could enable the possibility of long-term PFS for a greater number of R/R patients with MM who previously experienced poor outcomes. Second, the improvement in allo-SCT, especially haplo-SCT, could offer the possibility of a curative clinical outcome for a small number of patients with NDMM. Third, multicenter randomized clinical trials are needed to compare the outcomes of R/R MM cases treated with either CAR T-cell therapy or other targeted therapies, such as belantamab mafodotin and bispecific T-cell engager. Overall, further elucidation of the mechanisms of relapse and resistance to CAR T cells and auto-SCT/allo-SCT, the discovery of new biomarkers to direct therapy, and the design of new approaches for MM treatment, such as NKG2D-CAR-transduced natural killer cells [74, 90] and a novel CD38/CD3 bispecific T-cell engager [108], would help us improve outcomes through the realization of precision medicine for treating patients with MM.

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