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Review article

Exploring cellular immunotherapy platforms in multiple myeloma

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ABSTRACT

Despite major advances in therapeutic platforms, most patients with multiple myeloma (MM) eventually relapse and succumb to the disease. Among the novel therapeutic options developed over the past decade, genetically engineered T cells have a great deal of potential. Cellular immunotherapies, including chimeric antigen receptor (CAR) T cells, are rapidly becoming an effective therapeutic modality for MM. Marrow-infiltrating lymphocytes (MILs) derived from the bone marrow of patients with MM are a novel source of T cells for adoptive T-cell therapy, which robustly and specifically target myeloma cells. In this review, we examine the recent innovations in cellular immunotherapies, including the use of dendritic cells, and cellular tools based on MILs, natural killer (NK) cells, and CAR T cells, which hold promise for improving the efficacy and/or reducing the toxicity of treatment in patients with MM.

1. Background

Multiple myeloma (MM) is a hematological malignancy characterized by the abnormal proliferation of clonal malignant plasma cells [1,2]. The availability of new drugs such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs) has greatly improved the survival of patients with MM over the last decade. In comparison to traditional chemotherapy, PIs and IMiDs, which are frequently used in combination, have significantly enhanced the treatment of MM, yielding higher response rates, longer progression-free survival (PFS), improved overall survival (OS), reduced side effects, targeted therapy,

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personalization, and resistance reduction, leading to significantly improved outcomes for MM patients [3–5]. These treatments have now become the standard of care for MM patients. However, it is important to remember that treatment options are highly individualized and should be explored with a healthcare practitioner based on the patient's specific circumstances and disease characteristics [6,7]. Despite significant advances in treatment, most patients with MM eventually relapse and succumb to the disease [8,9]. T-cell dysfunction is a continuing challenge for the treatment of MM [10], as in advanced stages the immune system is often compromised, such that both T-cell function and the response to immunotherapies, such as checkpoint inhibitors, are reduced [11]. New strategies are therefore needed to enhance T-cell function in MM patients. Understanding the mechanisms of T-cell dysfunction could lead to strategies to improve T-cell function and in turn improve the response to immunotherapy, resulting in better outcomes for patients with MM (Fig. 1). This review focuses on commercial chimeric antigen receptor (CAR)-T cell, dendritic cell (DC), natural killer (NK) cell, CAR-NK cell, and marrow-infiltrating lymphocyte (MIL) therapies that are currently under evaluation in clinical trials for the treatment of MM as described in Tables 1–5.

2. CAR T-cell therapy

Cellular immunotherapies have changed the treatment landscape for patients with cancer [69]. Advances in adoptive T-cell therapy [70] have led to the development of several commercially available CAR T-cell therapies [71]. The use of CAR T cells in hematological malignancies has emerged as one of the most promising cellular immunotherapies. CD19-targeted CAR T cells are currently approved for the treatment of relapsed/refractory B-cell lymphoma, and B-cell acute lymphoblastic leukemia [72–74]. CAR T-cell therapy in myeloma is based on the optimization of a CAR construct that can specifically recognize myeloma surface antigens, such as B-cell maturation antigen (BCMA) or CD38. More recently, CAR T cells targeting BCMA have shown impressive results in patients with relapsed/refractory multiple myeloma (RRMM), with trials showing objective response rates (ORRs) of 73%–98% [75–77]. In recent years, anti-BCMA CAR T-cell therapy has yielded impressive outcomes in patients with RRMM, and its side effects are generally controllable. The Food and Drug Administration (FDA) has approved BCMA-targeted CAR T-cell therapies for patients with RRMM [75,76], including idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel). Idecabtagene vicleucel (Abecma), also known as bb2121, is a genetically modified autologous cell therapy that modifies T cells with a lentiviral vector encoding an anti-BCMA single-chain variable fragment, a CD137 (4-1BB) costimulatory motif, and a CD3ζ signaling domain [40]. A third BCMA-targeted

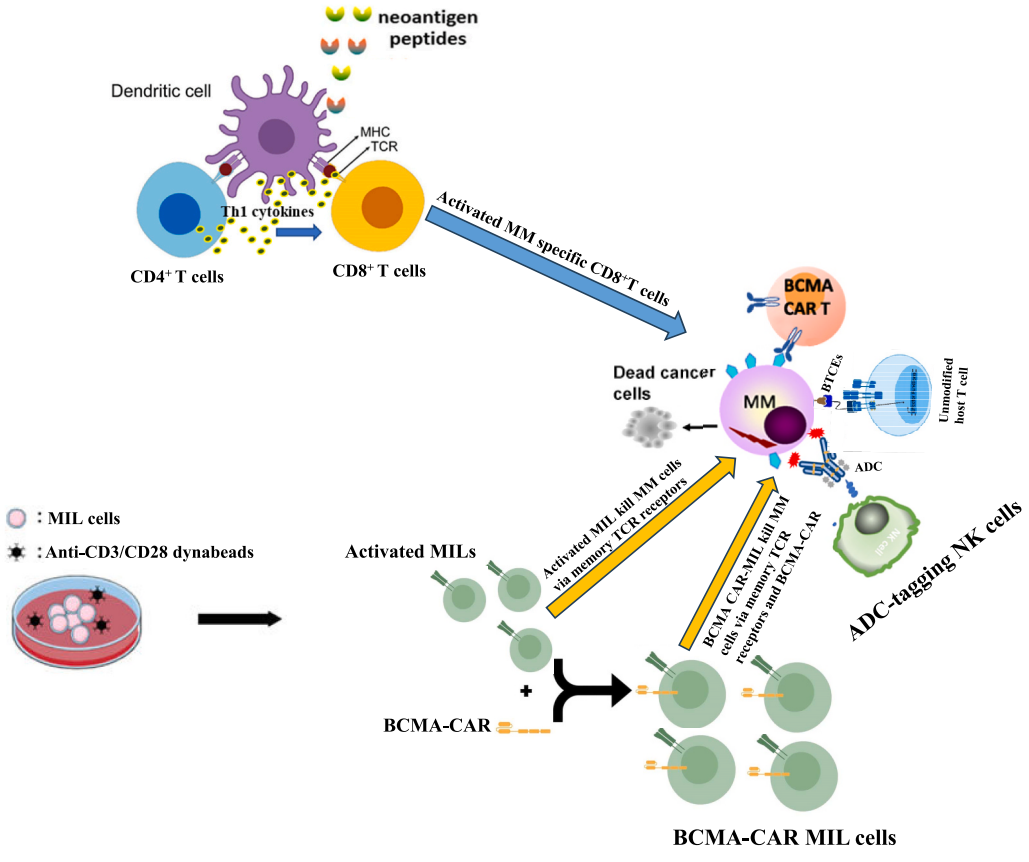


Fig. 1. (Graphical Abstract): Cellular immunotherapeutic strategies against multiple myeloma. BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MIL, marrow-infiltrating lymphocyte; NK, natural killer cell; ADC, antibody–drug conjugate.

Table 1
Clinical trials of cellular immunotherapy platforms for multiple myeloma.

TRIAL	REFERENCE	STUDY DESIGN	PLATFORM	INTERVENTION	STATUS	EFFICACY	ADVERSE EVENTS
NCT02064387	[12]	Phase I	ADCs	GSK2857916 (belantamab mafodotin/BLENREP)	Completed	ORR: 60% CR: 14% PFS: 12 months DOR: 14.3 months	Thrombocytopenia (35%), blurry vision (52%), dry eyes (37%), photophobia (29%)
NCT01001442	[13]	Phase I/ II	ADCs	BT062 (indatuximab ravtansine)	Completed	ORR: 5.9% CR: 0% PFS: 3 months OS: 26.7 months	Fatigue (47.7%), diarrhea (43.2%)
NCT06049290	[14]	Phase I/ II	BsAbs	LBL-034	Recruiting	N/A	N/A
NCT05182073	[15]	Phase I	CAR NK	BCMA targeting cyclophosphamide Fludarabine Daratumumab Bendamustine	Recruiting	N/A	N/A
NCT03940833	[16]	Phase II	CAR NK	BCMA CAR-NK 92	Recruiting	N/A	N/A
NCT05652530	[17]	Phase I	CAR NK	BCMA targeting	Recruiting	N/A	N/A
NCT05008536	[18]	Phase I	CAR NK	Anti-BCMA Fludarabine Cytoxan	Recruiting	N/A	N/A
NCT03090659	[19]	Phase I/ II	CAR T	LCAR-B38 M/CAR T BCMA targeting	Active, not recruiting	ORR: 88% CR: 68% VGPR: 5.3% PR: 14% MRD negative: 63.2%	CRS grade 1 (47%), CRS grade 2 (35%), CRS grade 3 (7%)
NCT03274219	[20]	Phase I	CAR T	Anti-BCMA bb21217	Completed	ORR: 69% sCR/CR: 28% Achieved $\geq$ VGPR: 58% MRD negative: 93%	CRS (75%), Neurotoxicity (15%)
NCT03548207	[21]	Phase I/ II	CAR T	JNJ-68284528	Completed	ORR: 97.9% sCR: 82.5% 27-month PFS: 54.9% OS: 70.4%	CRS (95%), neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%)
NCT02215967	[22]	Phase I	CAR T	Anti-BCMA Cyclophosphamide Fludarabine	Completed	ORR: 81% CR: 6.3% PFS: 7.8 months	CRS grade >3 (38%), ICANS grade >3 (19%), Serious adverse events (33.3%; 0%; 25%; 68.75%)
NCT03338972	[23]	Phase I	CAR T	FCARH143 Cyclophosphamide Fludarabine	Completed	ORR: 100% Median survival: 16 weeks	No DLTs, No CRS, No neurological toxicity
NCT02546167	[24]	Phase I	CAR T	CAR T-BCMA	Completed	ORR: 48% PFS: 65; 57; 125 days	CRS grade 3–4 (32%), neurotoxicity (12%)
NCT03430011	[25]	Phase I/ II	CAR T	Orva-cel (JCARH125) Anakinra	Completed	ORR: 91% sCR/CR: 39% VGPR: 25% PR: 27%	CRS grade $\geq$3 (2%), DLTs (4%)
NCT02728102	[26]	Phase II	DCs	DC/myeloma fusions GM-CSF Melphalan Lenalidomide	Completed	sCR/CR/VGPR at 1-year: 85.3%; 77.8% CR/sCR at 1-year: 52.9%; 50%	Post-transplant grade 3–4 toxicities (76.5%; 62.5%), Serious adverse events (2.94%; 8.11%; 2.86%)
NCT00566098	[27]	Phase I/ II	MILs	Melphalan PCV13	Completed	OR: 54% CR: 27% PR: 27% PFS: 25.1 months	All-cause mortality (45.5%), Nervous system disorders (4.55%)
NCT01858558	[28]	Phase II	MILs	Activated MIL No activated MIL	Completed	OS: 78.6% PFS: 21.8 months	All-cause mortality with activated MILs (1.43%), Serious adverse events (91.43%)
NCT02248402	[29]	Phase I/ II	moDCs	Vax-DC/UVB irradiated tumor MM cells Cyclophosphamide KLH	Completed	Immunological response: 77.8% Clinical benefit rate: 66.7% PFS: 2.9 months	Injection-site reactions (100%), myalgia (33.3%), fever (16.6%), chills (16.6%)
NCT04634435	[30]	Phase I	NKs	CIML NK/KP1237 IL-2	Recruiting	N/A	N/A
NCT02481934	[31]	Phase I	NKs	NKAEs Lenalidomide Bortezomib	Completed	Not Specified	Serious adverse events (40%), Other adverse events (40%)

(*continued on next page*)

Table 1 (*continued*)

TRIAL	REFERENCE	STUDY DESIGN	PLATFORM	INTERVENTION	STATUS	EFFICACY	ADVERSE EVENTS
NCT01729091	[32]	Phase II	NKs	Elotuzumab Lenalidomide Melphalan	Active, not recruiting	Achieved ≥ VGPR: 97% CR/sCR: 76% MRD negative: 75% 2-year PFS: 83% OS: 97%	No unexpected serious adverse effects

ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CIML NK, cytokine-induced memory-like NK cell; CR, complete response; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; DOR, duration of response; ICANS, immune effector cell-associated neurotoxicity; moDC, monocyte-derived dendritic cell; MRD, minimal residual disease; NK, natural killer cell; NKAE, activated and expanded NK cell; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

therapy that uses two BCMA-targeting single-domain antibodies, ciltacabtagene autoleucel, was approved based on the results of a phase I/II open-label trial in 97 heavily pretreated patients, and the ORR on treatment was 97%, with a stringent complete response (sCR) rate of 67% [41]. However, CAR T-cell therapy in clinical studies still faces major limitations due to complicated manufacturing procedures, insufficient homing to the target bone marrow site, and a narrow PFS rate in patients with relapsed disease. In addition, given the limited durability of CAR T-cell therapy responses in MM and high relapse rate of 40%–60% [78], it has been suggested that one of the barriers to cellular immunotherapy in MM is the poor infiltration of effector cells to tumor sites, which remains an issue with advanced CAR techniques [79]. Nevertheless, obstacles still remain, such as CAR T cell-associated toxicities, antigen escape [24], on-target off-tumor effects, and the immunosuppressive microenvironment [80]. A previous study reported that relapsed patients with RRMM experienced BCMA loss after treatment with anti-BCMA CAR T-cell therapy, but their MM cells maintained CS1 expression [81]. In addition, a recent clinical study using CS1-BCMA CAR T-cells showed an of ORR of 100%, sCR rate of 46%, minimal residual disease (MRD) negativity rate of 100%, and 1-year OS and PFS rates of 72.73% and 56.26%, respectively. Importantly, immune escape caused by target downregulation of BCMA and CS1 was not observed. However, the soluble BCMA level decreased and remained within normal levels in patients with sCR but increased slowly beyond normal levels in patients with very good partial response (VGPR) and partial response (PR) [82].

A phase I study of anti-BCMA CAR T-cell therapy in RRMM showed an ORR of 90% and a complete response (CR) rate of 43.3%. The median PFS and OS periods were 5.2 and 14.0 months, respectively. However, hematological toxicities were the most common events of any grade during treatment, with 29 patients (96.7%) developing cytokine release syndrome and only one patient (3.3%) experiencing neurological toxicities [18]. In addition, CRB-402 (NCT03274219) [77] was a multi-center phase 1 dose escalation trial of bb21217, developed from idecabtagene vicleucel, in 74 patients with RRMM who received ≥3 prior regimens of PIs and IMiDs or were double-refractory. The trial used bb21217 as a single infusion after lymphodepletion with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2). VGPR was obtained in 48% of RRMM patients, whereas 67% developed cytokine release syndrome and 22% developed neurotoxicity [83]. A phase I study using a human single-chain variable fragment (scFv) antibody-containing BCMA CAR T-cell construct showed no dose-limiting toxicity and good tolerance over a period of 28 days. The ORR was 100%, with no detectable abnormal bone marrow (BM) plasma cells (PCs). The M-protein level decreased by 73%, and BCMA CAR T cells remained detectable at 90 days after infusion. All patients survived at a median of 16 weeks. One patient relapsed, and a tumor biopsy showed a 70% reduction in BCMA antigen binding capacity. No cytotoxic T lymphocyte (CTL) response to the transgene product was identified in this patient [23]. The data suggested that construct-specific features and product formulation differences may significantly impact efficacy.

Although anti-BCMA CAR T-cell therapy has achieved impressive outcomes against RRMM in recent years, issues such as relapse, high manufacturing costs, and the long manufacturing cycle of autologous CAR T-cell therapy are still major issues restricting their accessibility. Therefore, the identification of novel MM antigens, optimal CAR structures, the application of dual-targeted CAR T cells, and combination therapy consisting of CAR T cells and other approaches are ongoing areas of investigation. Further advances are required to improve the durability of responses after CAR T-cell therapy, including enhanced patient selection, the development of novel CAR designs targeting multiple antigens to overcome the tumor microenvironment (TME), improved homing to target sites, and modification of the manufacturing procedure [84]. Training a workforce for a complex and evolving field requires innovative curriculum development [85]. New strategies and potential solutions continue to evolve, offering a path toward the development of more effective and safer future therapies [86,87].

3. Marrow-infiltrating lymphocytes

Adoptive immunotherapy therapies are currently generated from peripheral blood lymphocytes (PBLs) due to the convenience of obtaining large numbers of lymphocytes through leukapheresis. However, PBLs acquired in this manner may have a low level of endogenous tumor specificity, allowing tumor immune escape [88]. One strategy for increasing the tumor specificity of adoptive T-cell therapy is based on using tumor-infiltrating lymphocytes (TILs) from cancer patients, because tumor-specific memory T cells are more likely to be found in the TME but are inactivated due to its immunosuppressive effects [89]. Clinical studies of TILs have reported significant tumor specificity with measurable antitumor efficacy [70,90]. However, the applicability of TILs is limited, as they are not present in all solid tumors, often in low frequencies. Furthermore, TILs are frequently in a quiescent state (G0/G1), necessitating a longer period for selective expansion to ensure optimal expansion and activation of tumor specific memory T cells [91,92]. Thus, the

Table 2
Summary of cell-based immunotherapy for multiple myeloma.

Strategy	Potentials	Limitations	Latest preclinical advances
CAR-NK	BCMA CAR-NK cells recognize and eliminate BCMA-expressing myeloma cells [33–35] Optimize CAR construct [15,36,37] Generating CAR-NK cells from allogeneic or induced pluripotent stem cells (iPSCs) [15] Dual-targeting CAR-NK cells [33,35]	Immunosuppressive factors prevent CAR-NK activity [38,39] Off-target toxicity [39] Manufacturing challenges [39]	Optimization of CAR-construct and limitation of off-target toxicity by combining CAR-NK cells with mAbs or ICIs [39]
CAR T	Safety and efficacy confirmed by numerous clinical trials; FDA approval [40,41] Dual-target CAR T-cell therapy, CAR structure optimization, or novel therapeutic targets [42]	Insufficient MM homing capability [43] MM patients still experience recurrence/relapse or progression [43] High manufacturing costs and longer manufacturing cycle of autologous CAR T-cell products limit their accessibility [43]	A group in Baltimore, USA, generated low-affinity CD229+ CAR T cells and overexpressed c-Jun to retain effective tumor targeting and avoid off-tumor toxicity [44]
CAR-MILs	MILs recognize numerous tumor antigens of MM, thereby increasing myeloma targeting; therapeutic effectiveness with mild side effects and limited possibility of relapse/recurrence [45,46,47,48]	Lack of preclinical evidence [45,46,47,48]	N/A
NKs	Combination of adoptive NK-cell therapy with myeloma chemotherapy (IMiDs) is a promising approach for eliminating MM cells [49] Combination therapies including mAbs, ICIs, and antimyeloma conjugates provide a foundation for the development of NK-based therapy [49]	Inhibitory receptors, cytokines, and immunosuppressive cells in the TME can impair NK cell cytotoxicity and limit their antitumor activity [49] Short period until NK cell exhaustion *in vivo* requires persistent infusion of NKs [49] Limited tumor specificity [49].	CAR-NK is the main approach for NK-based therapy against MM [33–35] Recent studies attempted to optimize CAR-NK design and NK cytotoxicity against MM cells [33–35]
ADCs	Promising ongoing clinical trials for MM based on ADCs [50] Combinations of ADCs, IMiDs, and PIs mainly focus on and provide promising directions for MM therapy [50]	Effectiveness of ADCs can be limited by the heterogeneous expression of target antigens [50] Development of resistance in myeloma [50] Optimization of payload selection and potency is still in progress to increase safety [50] Limited TME penetration [50]	BCMA targeting (belantamab mafodotin) [51] CD38 targeting (TAK-169, TAK-573) [52,53] CD46 targeting (FOR46) [54] CD74 targeting (STRO-001) [55] CD138 targeting (indatuximab ravtansine) [56] CD56 targeting (lorvotuzumab mertansine) [57]
DCs	Ex vivo-generated moDCs loaded with autologous myeloma-associated antigens are a promising tool for use in clinical studies [29] Combining DC-based immunotherapies with conventional therapies, including chemotherapy, IMiDs (lenalidomide and pomalidomide) and ICIs, is the main strategy for future treatment [58]	Long-term clinical responses were quite unsatisfied [29]. DC vaccination broadly depends on immune checkpoints and TEM, which may elicit harmful effects in clinical studies [58]	Investigation of a DC vaccine transduced with an adenoviral vector encoding full-length survivin (Ad-S) with mutations neutralizing its antiapoptotic function to restore immune responses in myeloma patients undergoing ASCT [58]

ADC, antibody–drug conjugate; ASCT, autologous stem-cell transplantation; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; DC, dendritic cell; ICI, immune checkpoint inhibitor; IMiD, immunomodulatory drug; MIL, marrow-infiltrating lymphocyte; MM, multiple myeloma; mAb, monoclonal antibodies; NK, natural killer cell; PI, proteasome inhibitor; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; TME, tumor microenvironment; aAPC, artificial antigen-presenting cell.

Table 3
Future perspectives for cellular immunotherapies against multiple myeloma.

	DCs	aAPC	TCR engineering	CAR T	CAR NK	TILs	MILs	CAR-MILs
Target	Multiple HLA- restricted peptides	Multiple HLA- restricted peptides	HLA-restricted Ag	Surface Ag	Surface Ag	Endogenous Ags	Endogenous Ags	Endogenous Ags, plus Surface Ags
Gene modification	No	No	Yes	Yes	Yes	No	No	Yes
Cost	$$$	$$	$$$$	$$$$$	$$$$	$$$$	$$	$$$$
Efficacy	Promising	Promising	Promising	High, FDA approved	Promising High	Promising	Promising	Promising High
Toxicity	Low	Low	Low	High-CRS	Promising Low	Low	Low	Promising Low
Manufacturing	7 days	7–10 days	7–10 days	7–10 days	14–21 days	5–8 weeks	7–10 days	10–14 days
Ag-escape risk	Intermediate	Intermediate	High	High	High	Low	Low	Low

aAPC, artificial antigen-presenting cell; Ag, antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DC, dendritic cell; HLA, human leukocyte antigen; MIL, marrow-infiltrating lymphocyte; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes.

Table 4
Criteria for patient selection/recruitment for multiple myeloma immunotherapies.

	DCs	NKs	TCR engineering	CAR T	CAR NK	MILs and CAR-MILs
Age	≥18 [29,59]	≥18 [31]	≥18 [51,60]	≥18 [61–63]	≥18 [18,17]	≥18 [28]
ECOG performance status	≤2 [29,59]	0–2 [31]	0–2 [51,60]	0–2 [61–63]	0–1 [18,17]	0–2 [28]
Life expectancy		≥6 months [31].			Expected survival ≥3 months [18,17].	
History of active malignancy	RRMM Patients received thalidomide, bortezomib, lenalidomide-containing regimens [29]	With MM in 2nd or later relapse or showing resistance after 2 treatment lines [31]	HLA-A*0201 (HLA-A2.1) positivity by molecular subtyping [51,60]	Patients must have received at least 3 prior treatment regimens for multiple myeloma [61–63]	Received at least 2 prior lines of treatment, including proteasome inhibitor and immunomodulator [18, 17]	Patients must have had more than PR after last therapy [28]
Informed consent	Must be obtained [29,59]	Must be obtained [31]	Must be obtained [51,60]	Must be obtained [61–63]	Must be obtained [18,17]	Must be obtained [28]
Prior transplant	ASCT [29,59]	Eligible for, and willing to undergo, high-dose chemotherapy and ASCT [31]	May include prior auto-SCT but not prior allo-SCT [51, 60]	Without any myeloma therapy in the past 6 months, except if the last myeloma therapy was a CAR T-cell therapy [61–63]	Have received allogeneic hematopoietic stem cell transplantation in the past 3 months for the treatment of multiple myeloma [18,17]	Previous hematopoietic stem cell transplantation; patients can have had prior relapsed disease as long as no previous transplantation [28]
Major cardiac conditions	Uncontrolled or severe cardiovascular disease (cardiac ejection fraction <0.5, severe conduction disorder)			Echocardiography ≥45% within 6 weeks of treatment protocol start [61–63]		

ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; DC, dendritic cell; ECOG, Eastern Cooperative Oncology Group; HLA, human leukocyte antigen; MIL, marrow-infiltrating lymphocyte; MM, multiple myeloma; NK, natural killer cell; PR, partial response; RRMM, relapsed/refractory multiple myeloma; SCT, stem cell transplantation; TCR, T-cell receptor.

Table 5
Preclinical studies of CAR NK-cell therapy for multiple myeloma.

Year	Reference	Structure of the CAR construct	Obtained results
2014	Jiang et al. [64]	Anti-CD138-scFv (4B3)-CD3ζ	CAR expression: 95% Mean cytotoxicity against MM cells: <50%; against K562: >60%
2014	Chu et al. [65]	Anti-CS1-scFv-myc tag-CD28^{-}CD3 ζ	CS1-specific CAR ↗ IFN-γ secretion *in vitro*, killing of CS1^{+} myeloma NK-92-CS1-CAR efficiently eradicate human IM9 tumors
2021	Leivas et al. [66]	Anti- NKG2D-scFv (41BB-CD3z)	CAR expression: 80.3% (day 15) Cytotoxicity against MM: 100% (E:T = 8:1)
2022	Ng et al. [34]	Anti-BMCA-scFv (modified, CXCR4R334X-CD8^{-}CD3z)	CAR expression: 92% Co-expression of BCMA CAR and CXCR4: 82% Median survival time ↗ 46.5; 51.5; 62; 78.5 days (PBS, mGFP CAR-NK, anti-BCMA CAR-NK, CXCR4^{R334X} + anti-BCMA CAR)
2022	Reiser et al. [67]	FT555 (anti-GPRC5D-scFv): iPSC derived CAR-NK cell co-targeting GPRC5D and CD38	CAR-GPRC5D expression: >90% CAR against GPRC5D-positive MM.1S cells: ↗67.4% Control MM progression ≤42 days Survival rate ↗ 43 days
2022	Motais et al. [68]	Anti-BCMA-scFv (NK cells expressing soluble TRAIL)	CAR-NK-92-TRAIL expression: >90% Cytotoxicity against MM: ↗23%–63%
2022	Cao et al. [33]	Dual-target BCMA/GPRCD5-scFv (Allogeneic CAR-NK-cell therapy)	Not specified

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MM, multiple myeloma; NK, natural killer cell.

TIL expansion protocol addresses the heterogeneity of TILs that requires to achieve optimal *ex vivo* expansion and activation of TILs (7–8 weeks) that include high doses of interleukin (IL)-2, which cause exhaustion, and are costly [92].

Adoptive immunotherapy in MM based on MILs also holds promise. In MM, the BM plays the role of the TME and acts as a secondary lymphoid organ rich in central memory T cells (Tcm) and antigen-presenting cells (APCs) [93,94]. Abundant Tcm and APCs in the BM can lead to continuous exposure to malignant PCs, which eventually enriches and maintains myeloma-specific T cells with polyclonal antigenic specificity that are exhausted under the immunosuppressive effects of the TME. However, upon their activation and expansion, MILs may exhibit heightened tumor specificity and efficacy in MM due to the unique immunological properties of the BM [45]. Therefore, MILs offer a potentially more organic approach to adoptive immunotherapy compared to current PBL-derived approaches [95], with distinct advantages in terms of specificity and persistence. Like TILs, they are derived from the TME of MM patients, enabling a highly targeted, personalized approach [95,96], however, MILs, on the other hand, are derived from the BM of hematological cancers such as MM. MILs require a shorter culture protocol than TILs because of the properties of bone marrow's microenvironment and biology. Unlike solid tumors, which have low frequencies of infiltrating lymphocytes, the baseline of lymphocytes in BM is relatively high, potentially reducing the expansion time [97]. Furthermore, lymphocytes in the BM may already be activated due to the continuous surveillance of this immune-privileged site [97], leading to shorter expansion and activation *in vitro* stimulation compared to TILs. Moreover, they include abundant memory T cells with broad antigenic specificity and effective tumor cell recognition and killing capability [95]. The higher CD8:CD4 ratio and larger population of Tcm after the activation and expansion of MILs allows them to persist long after their injection. Furthermore, they can be obtained easily from the BM of patients with MM, and 100% of the harvested cells can be expanded successfully. MILs are also less cumbersome to culture, with a short expansion procedure (10–14 days) and the need for only low doses of IL-2, enhancing their anticancer potential and cost effectiveness [45]. Upon activation and expansion, they show heightened tumor specificity and persistence in the TME [45]. Moreover, MILs are derived from the BM and have the ability to penetrate deep into the TME, making them effective in targeting MM cells that other immune cells and immunotherapy platforms cannot reach [95]. A previous study demonstrated that MILs have a distinct advantage over PBLs due to their higher levels of CXCR4 expression [46]. This chemokine receptor plays a crucial role in the interaction between the BM stroma and T cells (SDF-1–CXCR4), allowing MILs to efficiently home to the BM and eliminate MM cells [45]. However, there are limited clinical data on the use of MILs against MM. Nevertheless, a previous study demonstrated the feasibility and efficacy of MILs against MM, revealing a robust correlation between clinical outcomes and tumor-specific activity, as well as the persistence of tumor-specific T cells in the BM after adoptive T-cell therapy [45]. When the MILs are ready, patients undergo a lymphodepleting conditioning regimen. Upon infusion, the MILs migrate directly to the tumor bed and eliminate MM cells [45]. This capability makes MILs a very attractive therapeutic option because they do not need to be directed toward the tumor [95]. In addition, as MILs recognize target antigens specific to the individual patient's tumor, off-target toxicity occurs much more rarely than with current CAR T-cell therapies. Several clinical investigations have demonstrated that MILs are safe and effective for the treatment of MM, with a significant reduction in tumor burden, improved quality of life, and prolonged survival compared to conventional therapies in MIL-treated patients [95,98]. Therefore, they offer an alternative to the limitations of current treatments for MM [99]. In a clinical study, Noonan et al. [45] treated 25 patients with either newly diagnosed or relapsed disease with infusion of a median of 9.5×10^8 autologous MILs, achieving at least a 90% reduction in disease burden and significantly increased PFS (25.1 months vs. 11.8 months; $P = 0.01$); this study highlighted the feasibility and efficacy of MILs as adoptive T-cell therapy for various hematological malignancies and possibly solid tumors infiltrating the BM.

4. Expanding and engineering MILs

Therapeutic MILs can be generated via expansion and genetic engineering to confer them with the desired attributes. By expanding MILs, it is possible to obtain a large population of cells able to break down the TME and recognize and attack myeloma cells robustly and specifically. Mononuclear cells are isolated from the BM of patients with MM and stimulated with anti-CD3/CD28 antibody-coated paramagnetic beads in the presence of cytokines, such as IL-2, IL-7, IL-15, and IL-21, which promote MIL proliferation and the development of $CD8^{+}$ Tcm as well as T-cell receptor (TCR) clonal diversity. MILs are continuously cultured for 7–14 days and split when T-cell blasts are observed. During cell harvesting, the paramagnetic beads are removed using a magnet (Fig. 2A). As MILs contain polyclonal Tcm populations that give them broader antigen recognition capability, they provide a powerful platform for CAR T cell-based genetic modification. The ability of CAR-MILs to effectively kill MM cells is derived from the fact that they include polyantigenic CTLs that can recognize a broad range of tumor antigens via polyclonal memory TCRs, and the CAR pathway, with strong recognition of tumor antigens via the scFv. This broader antigen recognition profile of CAR-MILs could prevent MM cells from evading the antitumor response, by concealing one target at a time, in contrast to CAR T-cell therapies, which are engineered to recognize only one, or possibly two, target tumor antigens (Fig. 2B).

The blood cancer treatment market is rapidly developing globally, with the FDA recently approving two CAR T-cell treatments for MM and various combination treatments, including primary treatments for MM and second-, third-, fourth-, and fifth-line treatments for patients whose disease does not respond to first-line therapy [100]. However, CAR T cells in the clinic and on the market are generated from activated peripheral blood T cells [101], as discussed above, and are designed to target only one or two tumor antigens, such that eventual cancer recurrence is likely. The ability of MILs to recognize numerous tumor antigens of MM increases their therapeutic effectiveness, with fewer side effects, and minimizes the possibility of recurrence. Therefore, CAR-MILs are expected to be a more powerful therapeutic platform than conventional CAR T-cell treatments. The technology enables any CAR construct against MM to be introduced into MILs, with CAR-MILs then produced using standard procedures for manufacturing CAR T cells. Indeed, as a

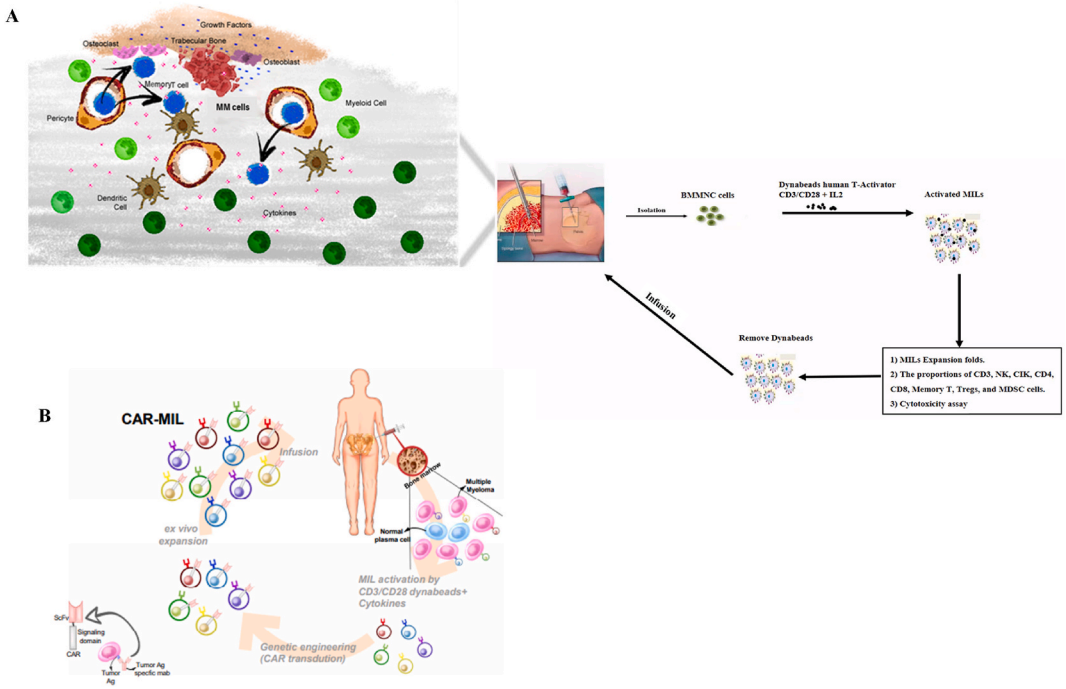


Fig. 2. Marrow-infiltrating lymphocyte therapy in multiple myeloma. (A) Schematic representation of the process used to generate marrow-infiltrating lymphocytes (MILs) for therapeutic use. Cells in the bone marrow (BM) of multiple myeloma (MM) patients include MM cancer cells, myeloid cells, and memory T cells, with diverse intercellular interactions mediated by different signals. For MIL expansion, BM mononuclear cells isolated from the BM of MM patients are expanded in culture with interleukin (IL)-2. Then, the MIL culture is expanded to a clinically relevant level and infused back into the patient. MILs use the natural memory T-cell receptors on their surfaces to recognize molecules on cancer cells (target antigens) that identify them as cancerous. When MILs come into contact with MM cells displaying target antigens, they launch a powerful attack to kill them. (B) CAR-MIL therapy against MM. Increasing the anticancer immune response of MILs requires overcoming the suppressive factors in the tumor microenvironment (TME) and improving the cancer cell killing capacity. The ability of tumor cells to downregulate their surface MHC expression can be counteracted by engineering MILs to express transgenic receptors and thereby recognize MM cells, which are otherwise undetectable by the immune system. Under this strategy, MILs are genetically modified to express chimeric antigen receptor (CAR) molecules and subsequently expanded. Then, autologous CAR-MIL cells are administered to the MM patient by intravenous infusion. When these cells come into contact with MM cells, they provide effective antitumor activity via polyantigenic cytotoxic T lymphocytes (CTLs) that leverage polyclonal memory T-cell receptor (TCR) and CAR pathways, with strong tumor antigen recognition via scFv.

proof of concept, an anti-BCMA CAR-MIL was successfully generated [47]. We are currently developing anti-BCMA dual--epitope-binding CAR-MILs for MM. The transduction efficiency was approximately 34%, with >100-fold expansion of BCMA CAR-MILs over a 21-day culture period. BCMA CAR-MILs were enriched with a higher proportion of $CD8^+$ Tcm (80%), whereas the proportions of $CD4^+$ T cells, regulatory T cells (Tregs), and checkpoint molecules (TIGIT, TIM3, and CD73) were not as high. In addition, BCMA CAR MILs showed potent cytotoxicity against MM cells, such as RPMI8226, U266B1, and autologous $CD138^+$ primary myeloma cells [102].

5. Bispecific T-cell engagers in MM treatment

Over the past decade, bispecific T-cell engagers (BTCEs) have been rapidly developed for the treatment of MM. BTCEs are composed of two scFvs connected by a protein linker [103]. These scFvs bind to MM antigens such as BCMA, CD138, or CD38 and the CD3 subunit of the TCR, forming an immune synapse that promotes tumor-specific T-cell activation and polyclonal expansion [104]. Importantly, BTCEs are independent of TCR specificity and do not require the addition of costimulatory molecules or peptide antigen presentation for target cell lysis [105].

A phase I/II clinical trial was conducted to assess the dose-limiting toxicities of BCMA/CD3 BTCEs, named REGN5458, which contain an Fc region with BCMA Fab and CD3 Fab domains. All patients with RRMM showed progression after three or more prior treatment lines. Two patients (50%) had MRD negativity after weekly administration of 6 mg of REGN5458, whereas five patients (71%) experienced treatment-emergent adverse events (NCT03761108) [106,107]. Another BCMA BTCE, TNB-383B, has the advantage of fully human scFvs within its structure. A clinical trial using TNB-383B was performed to investigate the MTD and pharmacokinetic profile of this BTCE in patients with RRMM (NCT03933735) [108]. Furthermore, a clinical study reported early results from a first-in-human study of BCMA–CD19 bispecific CAR T cells for patients with RRMM. Despite a relatively short disease evaluation time, BCMA–CD19 bispecific CAR T cells showed extraordinary safety and efficacy, with all five patients responding to the treatment; one patient achieved sCR, three achieved VGPR, and one achieved PR [109]. The development of BTCEs represents a huge breakthrough in achieving favorable clinical outcomes in treatment of MM. However, antigen loss and immunosuppressive factors, particularly upregulation of inhibitory immune checkpoint molecules, cause treatment failure in BTCE therapy, leading to the development of treatment resistance [110]. Therefore, numerous strategies for developing novel BTCEs with higher antigen avidities and multiple targets, as well as combination therapies, are being investigated to improve antitumor strategies focusing on BTCEs [111, 112]. We are optimistic that such knowledge will facilitate the evolution of antitumor strategies focusing on BTCEs.

6. Natural killer (NK) cells

Advanced cancer therapies combine chemotherapy and immunotherapy, with the goal of promoting synergistic therapeutic benefits and optimizing antitumor activity. Chemoimmunotherapy strategies offer a new framework for developing targeted cancer immunotherapy in which chemotherapeutic agents induce cancer cell death, and cancer immunogenicity provokes an immune response against the cancer cells. The chemotherapeutic agents are chosen to minimize adverse effects on immune cells, allowing the latter to maintain their lethality against cancer cells.

In the treatment of hematological malignancies using CAR T cells, it is evident that only clinical trials involving CD19 and/or BCMA demonstrated good outcomes, whereas other tumor-associated antigens (TAAs) did not [113]. However, the high relapse rate has raised concerns regarding CAR T-cell therapy [114,115]. NK cells are a subset of peripheral blood lymphocytes. As effector cells of the innate immune system, they have potent cytotoxic activity against infected cells and cancer cells. Unlike T or B cells, NK cells lack a unique antigen recognition receptor and do not require prior antigen sensitization or presentation by APCs. Their cytotoxicity depends on the complex interaction of germline-encoded activating and inhibitory receptors with ligands on target cells. Therefore, NK cells offer several advantages over T cells, including cytotoxic activity without prior antigen exposure or HLA restriction, as well as a lower risk of graft-versus-host disease (GVHD) [116]. *Ex vivo* activation and expansion of NK cells have been reported to have anti-MM effects [117]. However, clinical studies have reported disappointing results for adoptive autologous NK-cell therapy in cancer treatment [118]. The potential of combining NK-cell therapies with other treatment modalities for MM, such as autologous stem cell transplantation (ASCT) and treatment with mAbs such as daratumumab [119], elotuzumab [120], and isatuximab [121] to overcome this immunosuppression and boost the activity of NK cells has been investigated.

In MM, the tumor cells evade host immunity by activating tumor-suppressive pathways and suppressive cytokines, such as transforming growth factor-β, vascular endothelial growth factor, and IL10, causing effector cells to become dysfunctional. In patients with advanced MM, circulating NK cell numbers and function are suppressed. Numerous strategies have been developed to enhance the antitumor efficacy of NK-cell therapies, including overcoming TME suppressive factors, promoting NK-cell persistence *in vivo*, and inducing NK-cell trafficking to the TME. Recently, using NK cells expanded *in vitro* with K562 cells expressing OX40L ligand and membrane-bound IL-18/IL21, our group showed that robust cytolytic activities were activated against both MM cells [122] and the malignant cells of head and neck cancers [123]. In previous *in vivo* studies of MM-bearing mice, the combination of NK cells with daratumumab, bortezomib, and dexamethasone (DVd regimen) [117] or with daratumumab, lenalidomide, and dexamethasone (DRd regimen) [124] significantly increased the percentage of circulating NK cells, prolonged disease-free survival and OS, reduced the level of serum M-protein, and did not cause GVHD or cytokine release syndrome. In a phase I clinical trial, 12 patients with MM who underwent ASCT received *ex vivo* expanded and activated autologous NK cells. All patients who could be assessed showed objective, detectable responses after NK-cell infusions, defined as a reduced M-component and/or MRD [125]. Based on the findings of this clinical trial in which selected patients were injected with multiple doses of autologous NK cells, the authors concluded that this

strategy may be particularly suitable for patients with a low tumor burden, such as those in hematological remission but still positive for MRD. This rationale may also be applicable to other indications where tumor reduction is achieved by irradiation, surgical resection, and/or chemotherapy [126]. Therefore, we speculate that the effectiveness of the treatment in this study may have been attributable to the patient selection strategy, where subjects were given NK-cell infusions when in either subclinical relapse after CR, stable PR, or PR with asymptomatic progression [125]. Furthermore, this study utilized a "combination of three to four cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBorD). Patients underwent ASCT, and finally received an escalating dose of *ex vivo* activated and expanded autologous NK cells," which suppressed the MM microenvironment, allowing infused NK cells to migrate to the tumor bed and kill MM cells [125].

In another phase 1 study of MM treatment, 12 patients with MM received cord blood-derived NK cells in association with ASCT. The results showed an ORR of 83% and near CR in 67% of the cohort, with no evidence of GVHD [127]. In addition, a phase II study was performed to determine the efficacy of cord blood-derived natural killer (CB-NK) cells combined with elotuzumab/lenalidomide for patients with high-risk multiple myeloma (HRMM) undergoing ASCT. The study enrolled 30 patients with a median age of 63 years, with 80% receiving induction therapy with bortezomib or carfilzomib + lenalidomide + dexamethasone. After 3 months, 97% achieved $\geq$ VGPR (76% CR/sCR) and 75% were negative for MRD. At a median follow-up of 26 months (range: 12–44 months), only four patients showed disease progression (three of whom showed MRD positivity after ASCT), and the 2-year PFS and OS rates were 83% and 97%, respectively. No unexpected serious adverse effects attributable to NK cells were recorded [32]. The outcomes of clinical trials of NK cells against MM in different patients vary due to numerous factors, including the stage and genetic features of MM, the health of the patient, and the specific NK-cell therapy being used. Further evaluation of the safety and efficacy of NK-cell therapies for MM is ongoing (Tables 1–4).

7. Potential of antibody–drug conjugates (ADCs) in boosting the antimyeloma activity of NK cells

ADCs are targeted biopharmaceuticals that combine mAbs specific to tumor cell-surface antigens with powerful anticancer agents linked by a chemical linker [128]. ADCs bind to the specific antigen expressed on tumor cells via mAbs, and once internalized, initiate lysosomal degradation, which causes the release of the toxic payload within the tumor cells, resulting in cancer cell death [128]. In the treatment of MM, ADCs have been designed to target CD138, CD38, or BCMA [129]. These antigens are frequently overexpressed on the surface of MM cells, making them potential targets for ADCs. In a phase I study, monotherapy with belantamab mafodotin (belamaf, an ADC targeting BCMA, NCT02064387) was administered to patients with RRMM. Following dose escalation, the recommended dose was set to 3.5 mg/kg every 21 days. The ORR was 60% (6% PR; 40% VGPR; 9% CR; 6% sCR) and the PFS was 7.9 months after a median follow-up of 6.6 months [130]. A clinical study reported the use of belamaf as the first approved antimyeloma drug (ADC) in 2020 [131]. The DREAMM-2 trial involved 196 RRMM patients receiving the drug as a single agent. The ORR and PFS for the two cohorts receiving the drug at doses of 2.5 and 3.4 mg/kg were 31% and 2.9 months and 34% and 4.9 months, respectively. However, the FDA-required follow-up confirmatory trial (DREAMM-3; NCT04162210) comparing belamaf monotherapy to pomalidomide/dexamethasone failed to show an improvement in PFS, leading to the withdrawal of approval in November 2022. Despite this setback, several trials in the DREAMM series continue to compare belamaf with established antimyeloma therapies. Commonly reported adverse events include thrombocytopenia, blurred vision, and cough. The most common serious adverse events (SAEs) were pneumonia or lung infection and infusion-related reactions. Based on the potential of ADCs against MM, we anticipate that a combination of ADCs and NK cells has the potential to improve the therapeutic efficacy of both approaches [132]. ADCs target and destroy MM cells, whereas NK cells recognize and kill any remaining MM cells not targeted by the ADCs. This combined approach could help to overcome the development of resistance of MM cells to ADCs, deliver potent chemotherapeutic agents to target MM cells, and enhance the homing of injected NK cells toward TME sites without compromising their cytotoxic activity, ultimately increasing the combinatorial anticancer efficacy against MM. In contrast, the combination of NK cells with regular antibodies, such as CD38, BCMA, and SLAMF7 [133,134] is a promising strategy, as it enhances the antibody-dependent cell-mediated cytotoxicity (ADCC) of NK cells against MM cells. However, patients still relapse, partially due to suppressive factors in the MM microenvironment, as well as the reliance of mAbs on functional NK cells to mediate ADCC.

Based on the biological features of NK cells, CAR-NK cells genetically engineered against cancers are likely to be a promising therapeutic tool [135]. Due to the limited lifespan of NK cells *in vivo*, the safety of both NK cells and CAR-NK cells in clinical settings has been demonstrated [136–140]. Moreover, CAR-NK cells have the ability to kill cancer cells in a CAR-dependent (artificial) manner and through their natural cytotoxic activities (immunological synapse), such that a heterogeneous tumor can be eradicated despite the low-level expression of CAR-targeted antigens [141–144].

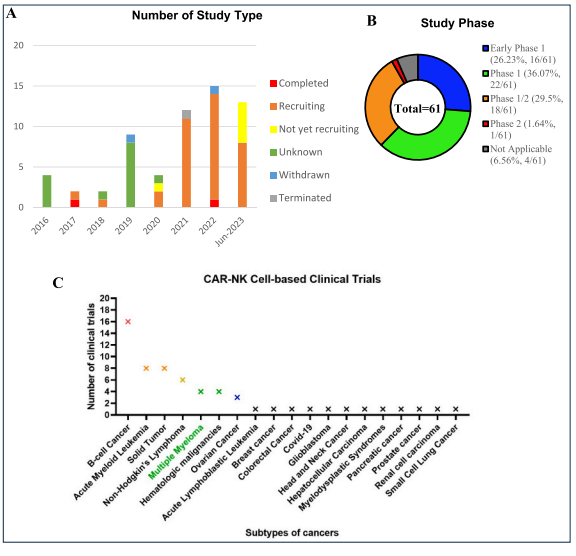
Many knowledge gaps remain to improve the efficacy and durability of the CAR-modified NK cell approach, including redirecting the specificity and precise homing of NK cells to tumors, and disrupting the TME to augment NK cell recruitment, metabolism, and cytotoxicity, all of which remain largely unexplored [145,146]. Given the complexity of the TME and the goal of maximizing patient benefit, CAR-NK-cell therapies can be combined with other traditional approaches to improve current anticancer treatment regimens [147–149]. Extensive research on CAR target recognition has focused on optimizing the intracellular signaling moiety to maximize immunomodulatory signals mediated by costimulatory molecules, which are commonly derived from the CD28 or TNFR gene families [43]. The core stimulatory molecule, CD3ζ, is essential for lymphocyte activation and promoting CD16-mediated ADCC in all CAR constructs [78].

However, numerous challenges in the use of CAR-NK cells have emerged, such as TME suppressive factors, tumor heterogeneity, silencing of targeted tumor antigens, loss of targeted antigens, and tumor heterogeneity [78]. Therefore, many aspects of CAR-NK cells must still be addressed, including improving CAR design for optimal NK-cell activation and cytotoxicity, overcoming tumor

suppression and escape, improving CAR-NK-cell persistence *in vivo*, and combining CAR-NK cells with other immunotherapeutic platforms and strategies to bolster CAR-NK cell production, storage, and delivery [84] (Fig. 3A–3D; Table 5). In a phase I study (NCT05182073) [15], FT576, a unique BCMA CAR-NK-cell therapy derived from an engineered induced pluripotent stem cell line, was administered as monotherapy or in combination with daratumumab in patients with MM. As of the 2022 data cutoff, no dose-limiting toxicities, cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, or GVHD events have been observed. Another trial (NCT03940833) [16] aimed to generate CAR-NK cells from the NK-92 cell line to assess the safety and feasibility of this therapy in RRMM patients. However, there have been no updates on this trial for the past 3 years, and no data have yet been reported.

8. Dendritic cell vaccination

DCs are APCs that play crucial roles in initiating and maintaining antigen-specific adaptive immunity [1,2,150]. DCs are concentrated during the development of monoclonal gammopathy of undetermined significance (MGUS) to MM, and play critical roles in the production of the immunosuppressive enzyme indoleamine-2,3-dioxygenase (IDO) [151] and adenosine (ADO) [152], compromising immune surveillance. During the development of MM, plasmacytoid DCs (pDCs) and myeloid DCs (mDCs) in the BM show high-level expression of programmed death-ligand 1 (PD-L1) [153] and transforming growth factor-β (TGF-β) [154], sustaining an immunosuppressive BM microenvironment. Cancer vaccines have been developed using patients' own DCs [1,2]. However, in MM, the efficacy of DC vaccines has been limited for several reasons. First, immunosuppressive factors secreted by myeloma cells act together with the TME to suppress DC function [155]. Second, the *ex vivo* DC culture process is costly, time-consuming, and requires specialized infrastructure, such that DC vaccination has seen only limited clinical use. Third, only 4% of injected DCs migrate to the lymph nodes to perform their functions [156,157]. Fourth, the efficacy of a DC vaccine is highly dependent on the exhaustion level of the patient's immune system [1,2]. For successful DC vaccination strategies, the tumor antigen, the potency of the DC vaccine formulation, the mode of delivery, the use of adjuvants and immunomodulation drugs, and the treatment schedule must all be taken into consideration. Antigen selection is crucial for inducing myeloma-specific CTL responses [1,2,158]. Among the tumor-associated antigens (TAAs) identified in MM, BCMA and CS1 are restrictively expressed at high levels in both normal and malignant PCs, making them potential target antigens for MM [113,159]. However, the immune response to a single TAA is generally poor, because MM cells can escape immune recognition by downregulating the antigen over time [113,159]. To address this issue, DCs have been loaded with whole myeloma cells to enhance the antitumor immune response while preventing tumor cell immune escape [155,160]. Our group generated potent DCs loaded with dying myeloma cells, which induced myeloma-specific CTLs with strong Th1 polarization. Using this strategy, we reported a strong antimyeloma effect of DC vaccination combined with lenalidomide [161,162], pomalidomide [160], or checkpoint blockade in a murine myeloma model [163,164]. These enhancements of DC vaccination may hold promise for the development of therapeutic strategies capable of inducing myeloma-specific immune responses without significant adverse effects. However, despite the investigation of numerous DC-based therapies in clinical trials against MM over the past decade, long-term clinical outcomes have been unsatisfactory [165] (Tables 1 and 2). Similarly, data from the phase I/IIa study of patients with relapsed/refractory MM (RRMM) treated with DCs loaded with myeloma cells showed that local reactions at the injection site and infusion-related reactions were common toxicities of immunotherapy using VAX-DC/MM [29]. Vaccination was well tolerated without significant toxicity or evidence of autoimmunity. The majority of patients (77.8%) who received 10×10^6 cells exhibited an



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Clinical trials of CAR-NK cell therapy for multiple myeloma

	Title	Start date	Status	Interventions	Phase	Identifier	Locations
1	Anti-BCMA CAR-NK Cell Therapy for the Relapsed or Refractory Multiple Myeloma	October 1, 2021	Recruiting	Anti- BCMA CAR-NK Cells Drug: Fludarabine Cytoxan	I	NCT05008536	China
2	Clinical Study of the Safety and Efficacy of BCMA CAR-NK	November 13, 2022	Recruiting	Anti- BCMA CAR- NK Cells	I	NCT05652530	China
3	Clinical Research of Adoptive BCMA CAR-NK Cells on Relapse/Refractory MM	May 2019	Unknown status	Anti-BCMA CAR-NK 92 cells	II	NCT03940833	China
4	FT576 in Subjects with Multiple Myeloma	November 24, 2021	Recruiting	Allogenic anti-BCMA CAR NK cells Drug: Cyclophosphamide Fludarabine Daratumumab Bendamustine	I	NCT05182073	United States

Fig. 3. CAR-NK cell clinical trials. (A) CAR-NK cell-based cancer immunotherapy clinical trials. (B) State of CAR-NK cell-based clinical trials against multiple myeloma (MM) and other hematological malignancies. (C) Detailed summary of current clinical trials of CAR-NK cells in cancer immunotherapy. (D) Table of clinical trials of CAR NK-cell therapy for MM.

immunological response. However, this immunological response did not lead to remarkable improvements in clinical responses [29]. In an alternative approach, neoantigens expressed only on tumor cells and not on normal cells, thereby avoiding "off-target" damage, represent an ideal tumor antigen source for DCs [166]. In general, neoantigens are novel antigens that are specific to each cancer patient, and their selection is an important step in developing personalized cancer therapy and has potential to improve the efficacy of cancer immunotherapy [166] (Fig. 4). Previous studies have revealed the potency of DCs in priming neoantigens to T cells and in eliciting a specific immune response in patients with related mutations [167]. Various approaches have been evaluated to improve the efficacy of DC vaccines, including tumor antigen cocktails, genetic engineering, molecular biological modifications, and combinations with other agents [168]. Our group has also generated novel multipotent DCs by supplementing the peripheral blood mononuclear cells (PBMCs) of MM patients with IL-15. After 6 days of incubation, the IL-15 DCs exhibited outstanding activation of autologous T cells, cytokine-induced killer cells, and NK cells, as well as strong cytotoxicity against MM cell lines and $CD138^+$ autologous primary myeloma cells [169]. Programmed cell death protein 1/programmed cell death ligand 1 (PD - 1/PD - L1) has been identified as a negative immunomodulator that promotes MM development and evasion [170]. The high expression of PD-L1 on myeloid DCs in BM during MM development poses a significant treatment challenge, as multiple clinical trials using PD-1/PD-L1 checkpoint blockades in MM have shown poor outcomes [153]. Despite this, the CRISPR/Cas9 gene editing technique holds great potential for maximizing PD-1/PD-L1 deletion at the genomic level by directly editing PD-1/PD-L1 and indirectly regulating antigen presentation to improve the function of immune cells, as well as combating tumor immunosuppression factors [171]. Utilizing CRISPR/Cas9 to disrupt PD-L1, along with carefully designed personalized DC vaccines in combination with other treatment agents, could represent an effective approach to treating patients with MM and other malignancies. A schematic representation of enhanced DC vaccination strategies is provided in Fig. 5.

Nanotechnology has shown promise in improving myeloma treatment outcomes in both preclinical and clinical investigations [172]. A phase II clinical study of patients with RRMM treated with Doxil and bortezomib revealed a 50% response rate and a median PFS of 6.5 months [173]. Furthermore, a phase I study with 32 patients with RRMM found a 78% response rate and a favorable safety profile for nanoparticle albumin-bound paclitaxel in combination with lenalidomide and dexamethasone [174]. However, further studies are needed to understand potential adverse events and optimize treatment efficiency. Recent advances in nanomaterials have led to the development artificial APCs (aAPCs) as an option for generating tumor-reactive T-cell immunity [175,176]. In these strategies, nanoparticles enable the codelivery of antigens and adjuvants, in turn stimulating antigen-specific $CD8^+$ T-cell immune responses. aAPCs are biomimetic particles that mimic natural APCs by presenting an antigen recognition signal ("signal 1") and a costimulatory signal ("signal 2"), such as anti-CD28, to T cells on a synthetic particle core. aAPCs can be engineered with a flexible platform for enhanced immune system activation. Specifically, aAPCs can be designed to display specific tumor antigens, allowing for controlled and prolonged antigen release, which can be more effective in eliciting a robust specific immune response. aAPCs can also be equipped with costimulatory molecules to boost T-cell activation. Furthermore, surface modifications on nanoparticles can be designed to target specific cell types or tissues, improving the precision of immune system activation. aAPCs represent an off-the-shelf approach that can overcome the limitations of autologous culture strategies [175]. This improvement in DC vaccination may result in the development of cell therapy tools capable of inducing myeloma-specific immune responses without major side effects (Fig. 6). This approach has great potential for the development of next-generation T cell-based myeloma immunotherapy. A previous study

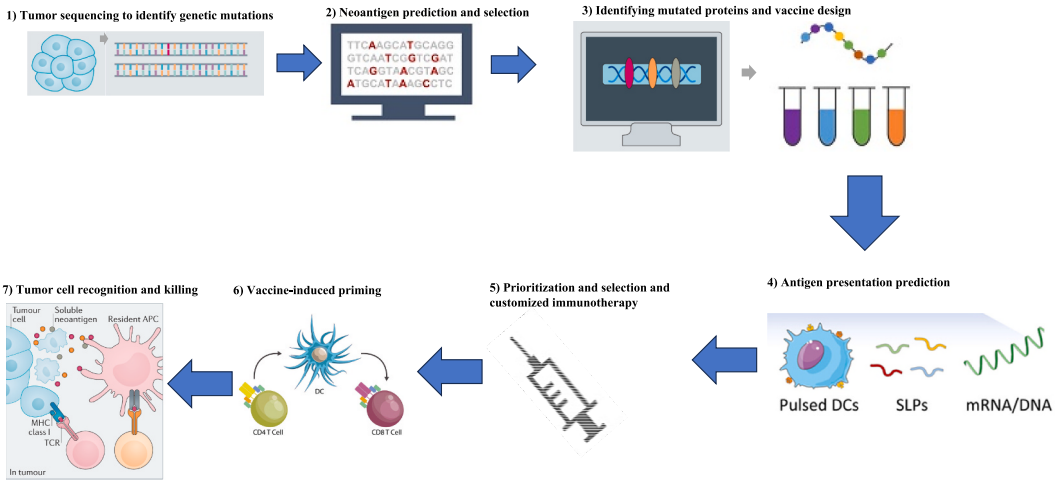

Fig. 4. Processes for obtaining and selecting neoantigens. 1) Tumor sequencing to identify genetic mutations, including single nucleotide changes (point mutations), insertions, deletions, and other alterations. 2) Identifying mutated proteins: once mutations are identified, the next step involves predicting which of these mutations will lead to the generation of neoantigens. 3) Antigen presentation prediction: bioinformatics methods are employed to predict whether a neoantigen will be efficiently presented by MHC molecules. 4) Prioritization and selection: the identified neoantigens are prioritized based on factors such as a predicted immunogenicity, MHC binding affinity, and expression levels in tumor cells. 5) Customized immunotherapy: the prioritized neoantigens are used to develop personalized cancer vaccines or tailor adoptive cell therapy to the individual patient.

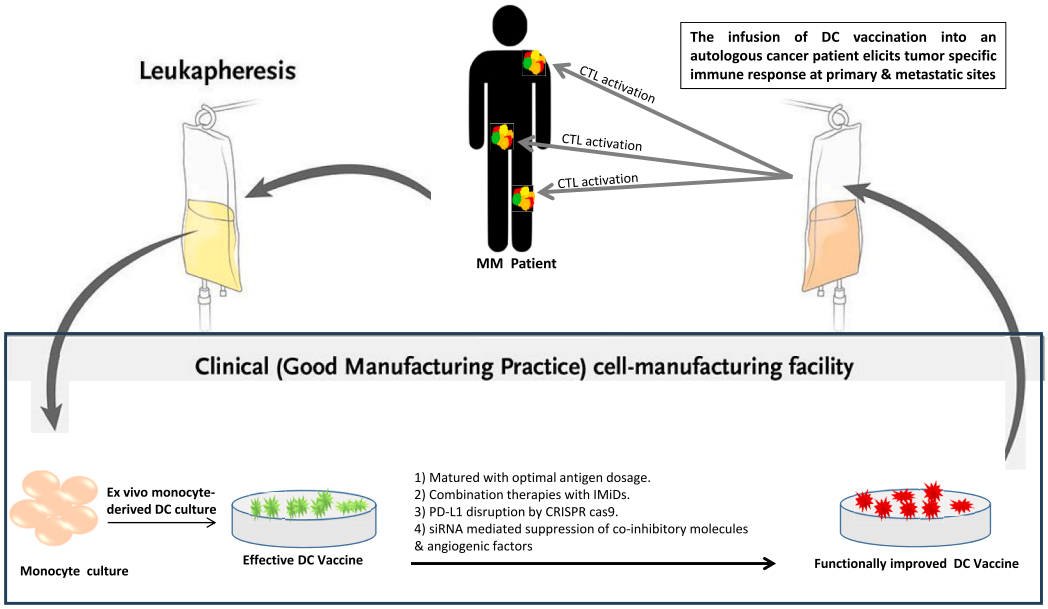

Fig. 5. Dendritic cells (DCs) generated ex vivo from peripheral blood monocytes of multiple myeloma patients and recovery of dysfunctional DCs by stimulation with appropriate cytokines and pulsing with optimal doses of tumor antigens. A combination of DCs and immunomodulatory drugs (IMiDs) restores the function of these cells by inhibiting immunosuppressive molecules and checkpoint inhibitors using genetic engineering and molecular biology approaches. Functionally active DCs can then be used to vaccinate patients to induce an effective antigen-specific antitumor immune response.

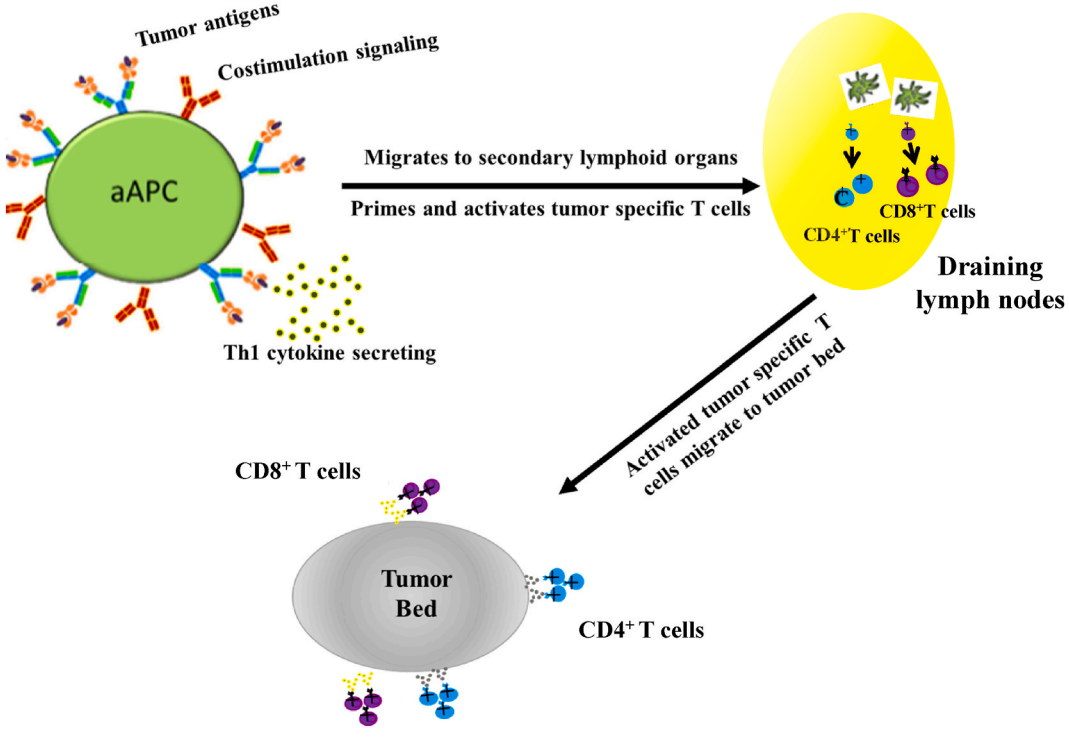

Fig. 6. Anticancer immune responses are triggered by artificial antigen-presenting cells. Optimized artificial antigen-presenting cells (aAPCs) that present tumor antigen, costimulatory signals, and Th1-polarizing cytokine-secreting signals can be used to stimulate the activation of antigen-specific $CD8^+$ and $CD4^+$ T cells against cancer cells. Additional advantages of aAPCs include their ability to overcome the negative effects of the tumor microenvironment (TME), minimal toxicity, lack of graft-versus-host disease induction, and cost effectiveness.

demonstrated that an aAPC synthesized from streptavidin-coated polystyrene particles evoked extremely strong memory $CD8^+$ T-cell responses against myeloma [177]. Although aAPC-based nanoparticles have not been used in clinical studies in MM, they have been shown to have potent antitumor effects in many cancer types, including melanoma [178]. A clinical-grade and good manufacturing practices (GMP)-quality K562-based aAPC-A2 line, clone 33, was used to expand MART-1-specific T cells against advanced melanoma [179]. The K562-aAPCs were transfected with four non-retroviral plasmids encoding HLA-A*02:01 (A2), CD80, CD83, and a puromycin resistance gene. Compared to the natural DC expansion platform, aAPC-A2 clone 33 similarly expanded MART-1-specific T cells from both healthy donors and patients with metastatic melanoma (19%–49% tetramer-positive) [179,180]. However, the K562 aAPC platform has not been widely used for cancer therapy as it was derived from a malignant clone. Although K562-aAPCs are irradiated before coculture with T cells such that none are detected after T-cell expansion, there are reasonable reservations about infusing T-cell products with a malignant cell line into cancer patients.

9. Conclusion

Recent advances in cellular immunotherapy, including CAR T-cell and CAR NK-cell therapies, have significantly impacted the treatment of MM, particularly in cases of RRMM. Ongoing and future multicenter randomized clinical trials will evaluate the outcomes of patients treated with CAR T-cell therapy or other targeted therapies. Novel approaches such as the use of MILs and CAR-MILs, along with novel BTCEs, hold great promise for improving outcomes and providing precision medicine for RRMM patients. In conclusion, cancer immunotherapy has demonstrated substantial potential for treating MM. The rapid evolution of technologies, such as DC vaccines, NK vaccines, CAR T cells, and CAR-NK cells, supports the development of advanced cancer treatment strategies. Although CAR T cells currently hold promise in the treatment of hematological malignancies, including MM, their existing limitations, such as toxicities, high relapse rates, and resistance, underscore the necessity of developing engineered CAR T cells that are more effective for therapeutic applications. Enhancing the efficacy and persistence of CAR T cells will be crucial to reestablishing an immune response against tumors. Moreover, addressing the specific challenges of CAR T cells in MM, such as improving trafficking and infiltration and enhancing resistance to the TME, remains a focus for ongoing research. The BM of patients with MM represents a TME with a unique immunological environment that contains inactive polyclonal memory T cells. The *ex vivo* activation of these cells in the BM of patients with MM may be effective to eradicate myeloma cells. MILs therefore possess many of the properties needed for adoptive T-cell therapy against MM. The specificity and persistence of MILs in the TME allow MILs to recognize and attack cancer cells that are often inaccessible to other forms of immunotherapy, making them an attractive option for the treatment of MM. Engineering MILs with an arm of scFv CAR to produce CAR-MILs will improve the recognition and destruction of myeloma cells by polyantigenic CTLs via polyclonal memory TCR and CAR pathways. CAR-MIL therapy therefore offers a promising option for the treatment of patients with MM.

Data availability statement

The data will be made available on request to the corresponding author.

CRediT authorship contribution statement

Manh-Cuong Vo: Writing – original draft. **Sung-Hoon Jung:** Writing – review & editing, Writing – original draft, Conceptualization. **Van-Tan Nguyen:** Writing – original draft. **Van-Dinh-Huan Tran:** Writing – original draft. **Nodirjon Ruzimurodov:** Writing – review & editing. **Sang Ki Kim:** Writing – review & editing. **Xuan-Hung Nguyen:** Writing – review & editing. **Mihee Kim:** Writing – review & editing. **Ga-Young Song:** Writing – review & editing. **Seo-Yeon Ahn:** Writing – review & editing. **Jae-Sook Ahn:** Writing – review & editing. **Deok-Hwan Yang:** Writing – review & editing. **Hyeoung-Joon Kim:** Writing – review & editing. **Je-Jung Lee:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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