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Immunotherapy in hematologic malignancies: achievements, challenges and future prospects

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The immune-cell origin of hematologic malignancies provides a unique avenue for the understanding of both the mechanisms of immune responsiveness and immune escape, which has accelerated the progress of immunotherapy. Several categories of immunotherapies have been developed and are being further evaluated in clinical trials for the treatment of blood cancers, including stem cell transplantation, immune checkpoint inhibitors, antigen-targeted antibodies, antibody-drug conjugates, tumor vaccines, and adoptive cell therapies. These immunotherapies have shown the potential to induce long-term remission in refractory or relapsed patients and have led to a paradigm shift in cancer treatment with great clinical success. Different immunotherapeutic approaches have their advantages but also shortcomings that need to be addressed. To provide clinicians with timely information on these revolutionary therapeutic approaches, the comprehensive review provides historical perspectives on the applications and clinical considerations of the immunotherapy. Here, we first outline the recent advances that have been made in the understanding of the various categories of immunotherapies in the treatment of hematologic malignancies. We further discuss the specific mechanisms of action, summarize the clinical trials and outcomes of immunotherapies in hematologic malignancies, as well as the adverse effects and toxicity management and then provide novel insights into challenges and future directions.

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INTRODUCTION

Cancer immunosurveillance is a process in which multiple innate and adaptive immune effector cells and molecules are involved in the recognition and killing of cancer cells.[1] Extrinsic immune stress can either prevent tumor growth, development and survival or promote tumor growth by both sculpting the immunogenicity of the tumor or inhibiting the anti-tumor immune response.[1,2] Immune editing is considered one of the key parts of why tumors could evade the surveillance and lie dormant in the host body for years before re-emerging through the "equilibrium" and "senescence".[3] With the growth of poorly-immunogenic variants and the destruction of the host immune system, cancer cells ultimately evade immunosurveillance.[4] Cancer cells employ many strategies to suppress the immune system of the human body, so that they can survive in every stage of the anti-tumor immune responses.[5] The generation of anti-tumor immune response is a complicated and multi-step process and Chen et al. refer to these steps as the "Cancer-Immunity Cycle".[6] As for cancer patients, the "Cancer-Immunity Cycle" does not perform optimally. Any abnormality in these steps can lead to the failure of the "Cancer-Immunity Cycle" and consequent cancer immune evasion.[7] Immunotherapies could fight against cancer by harnessing the immune system and restoring anti-tumor immunity.[8] Constructed over decades, immunotherapies have begun to demonstrate such promising results in treating cancer patients and have been selected as the "Breakthrough of the Year for 2013".[8–10]

Hematologic malignancies refer to malignant diseases originating from the lymphohematopoietic system and may involve all systems and organs throughout the body. Hematologic malignancies mainly include acute leukemia, chronic leukemia, lymphoma, multiple myeloma (MM), myelodysplastic syndrome (MDS), and myeloproliferative neoplasm (MPN). Acute lymphoblastic leukemia (ALL) is characterized by the abnormal proliferation of a huge number of immature lymphocytes.[11] Acute myeloid leukemia (AML) is the most commonly occurring acute leukemia in adults and its incidence increases with age. As a result of genetical mutations in hematopoietic stem/progenitor cells, AML is a highly heterogeneous disease.[12,13] Lymphomas are typically divided into two categories, Hodgkin lymphoma (HL, which accounts for about 10% of all lymphomas) and non-Hodgkin lymphoma (NHL).[14] NHL is the most prevalent kind of lymphoma arising from lymphocytes that are at various stages of development and the characteristics of the specific lymphoma subtype reflect those of the cell from which they originated.[14] Diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL) represent the most common types of NHL. HL, also known as Hodgkin's disease, is a rare type of lymphoma with unique histologic, immunophenotypic and clinical features.[15,16] HL consists of two discrete disease entities: classical HL (cHL), which accounts for the majority of HL cases and nodular lymphocyte predominant HL.[16] MM, MDS and MPN are most common in elderly patients. MM accounts for about 10% of hematologic malignancies and cannot currently be cured. It typically begins as an asymptomatic precursor, either a monoclonal gammopathy of undetermined significance or smoldering

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multiple myeloma.[17] MDS is a clonal disorder characterized by ineffective hematopoiesis and a tendency to evolve into AML.[18] With increasing advances in chemotherapy, radiotherapy and targeted therapy, the overall response rate (ORR) of cancer patients has improved significantly. Historically, multi-drug chemotherapy has been the cornerstone of the treatment of both pediatric and adult patients with hematologic malignancies. However, over the past decade, many patients still face treatment failure due to relapse and resistance. The molecular characteristics of hematologic malignancies are highly heterogeneous, leading to considerable challenges in precision medicine and individualized treatment.

With the potential to induce long-term remission in patients with refractory or relapsed (R/R) hematologic malignancies, immunotherapy has already led to a paradigm shift in cancer therapy and tremendous success in the clinic. Furthermore, hematologic malignancies in this setting have some unique characteristics that make these cancers well-suited as targets for immunotherapy.[19] Immune cells and cancer cells are in constant interconnection with each other within the hematopoietic system, enabling an environment that is conducive to immune surveillance. Since the cellular origins of malignancies are the same as that of the immune system, the nature of these cancer cells is immunostimulatory. However, this may meanwhile lead to deficit and hindered immune responses. There has been accelerating advancement of cancer immunotherapies based on various strategies to harness the host immune system. Different immunotherapeutic approaches have their advantages but also shortcomings that need to be addressed. This review will provide perspectives on the applications and clinical considerations of immunotherapies so that clinicians can acquire timely information about such revolutionary therapeutic options. Here, we first outline the recent advances made toward understanding multiple categories of immunotherapies in the treatment of hematologic malignancies. We further discuss the specific mechanisms of action, summarize the clinical trials and outcomes of immunotherapies in hematologic malignancies, as well as the adverse effects (AEs) and toxicity management and then provide insights into future directions.

THE HISTORY OF IMMUNOTHERAPY IN HEMATOLOGIC MALIGNANCIES

As for the field of treating hematologic malignancies, immunotherapy mainly involves targeted antibodies, immune checkpoint inhibitors (ICIs), tumor vaccines, adoptive cell therapy (ACT), and stem cell transplantation (Fig. 1a). The journey of the history of immunotherapy for hematologic malignancies is summarized in (Fig. 1b). The allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the oldest forms of cancer immunotherapy.[20] The allo-HSCT was first applied to disease treatment in 1968 by E. Donnall Thomas, who would later win the Nobel Prize for being a pioneer in this technology and is praised as "the father of stem cell transplantation".[20] The allo-HSCT was primarily performed for treating leukemia in 1975 and lymphoma in 1978. Since then, HSCT has been used worldwide to treat serious blood disorders. Although it has been referred to as "the bluntest weapon of chemotherapists", as it indeed aims to eradicate and restore the hematopoietic and immune systems, it still occupies a pivotal position and gives patients the possibility of a cure. It wasn't until the end of the 20th century that new immunotherapy approaches emerged. Rituximab, a kind of anti-CD20 monoclonal antibody (mAb), was the first to be approved by the United States Food and Drug Administration (FDA) for the treatment of cancer in 1997 and since then has become the prototype for anti-CD20 mAbs and the backbone treatment regimen for B-cell malignancies, such as DLBCL, CLL (chronic lymphoblastic leukemia) and FL.[21] As well, the rituximab, combined with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen, has become the first-line therapy for patients with NHL.[22] Meanwhile, more types of mAbs have been developed, such as tafasitamab (anti-CD19 mAb) for DLBCL,[23] daratumumab (anti-CD38 mAb) for MM,[24] and lintuzumab (anti-CD33 mAb) for AML.[25] However, for R/R patients, mAbs often lose their clinical effectiveness and the development of bispecific antibodies (bsAbs) may allow for the continuation of treatment. Blinatumomab, an anti-CD3/CD19 BiTE (bispecific T cell engager), was the first FDA-approved BiTE for the treatment of R/R precursor B-cell ALL (pre-B-ALL) and has also achieved remarkable curative effects.[26] Over the past several decades, antibody-drug conjugates (ADCs) have been evaluated in a variety of clinical trials of hematologic malignancies. The brentuximab vedotin was approved by the FDA in 2011 for treating relapsed HL and systemic anaplastic large cell lymphoma (SALCL).[27,28] WT1 (Wilms' tumor gene 1) peptide-based tumor vaccine was first used in patients with overt leukemia from MDS or MDS with myelofibrosis in the year 2002.[29,30] As another rising star in immunotherapy, ICIs have entered the field of treatment for hematologic malignancies due to their great success in solid tumors. PD-1/PD-L1 (programmed death receptor 1, programmed death receptor ligand 1) inhibitors play a notable clinical role in B-cell lymphoma, especially in HL.[31] CTLA-4 (cytotoxic T-lymphocyte antigen number 4) inhibitor also demonstrates certain curative effects in patients with HL and AML.[32] There're lots of clinical trials of these drugs applied to different kinds of hematologic malignancies to overcome resistance and relapse. ACT is the most popular immunotherapy for patients with R/R hematologic malignancies, such as TCR-T (T cell receptor-engineered T) cell, γ/δ-T (gamma/delta T) cell, NK (nature killer) cell and CAR-NK (chimeric antigen receptor nature killer) cell and especially CAR-T (chimeric antigen receptor T) cell therapy.[33–35] Fred Hutchison Cancer Institute used CAR-T cells for the first time to treat B-cell lymphoma and proved its safety in the year 2008. And in the year 2010, two patients with CLL first received CAR-T transfusion and achieved CR (complete remission) and the CAR-T cells were still detected in vivo after 10 years of follow-up.[36] In 2012, Emily, an American patient with B-ALL, received CAR-T therapy and was cured. She has been disease-free for almost 11 years up to now. The development of CAR-T therapy has been greatly boosted due to the launch of large clinical trials, such as axicabtagene ciloleucel and tisagenlecleucel, as well as the FDA's approval of the first commercialized CAR-T cell product in 2017. At present, CAR-T therapy has achieved remarkable results in R/R ALL, CLL, NHL, and MM.[37] There are many CAR targets for each malignant disease and the number of treatment lines is gradually advancing. In summary, immunotherapy has achieved rapid development in recent years, which provides more possibilities and hopes for the cure of hematologic malignancies.

OVERVIEW OF IMMUNOTHERAPIES IN HEMATOLOGIC MALIGNANCIES

HSCT

HSCT is an effective means of curing a range of hematologic diseases. It is done by harvesting functional hematopoietic stem cells from the patients or a healthy donor and transplanting them to the patients to replace their dysfunctional blood system. Initially, bone marrow was considered as a source of stem cells for transplantation. However, within the last two decades, peripheral blood stem cells have replaced bone marrow stem cells and become the main stream.[38] The replacement indicates no impact on overall survival (OS) except a greater risk of graft-versus-host disease (GVHD).[38] Fortunately, the management of GVHD is strict and upgraded continuously.[39] The allo-HSCT is usually considered as a preferred choice for hematologic malignancies.[40,41] But due to the greater risk of GVHD, allo-HSCT is still restrictive to the patient's own status. This led to the emergence of reduced-intensity stem cell transplantation (RIST), which is associated with less morbidity

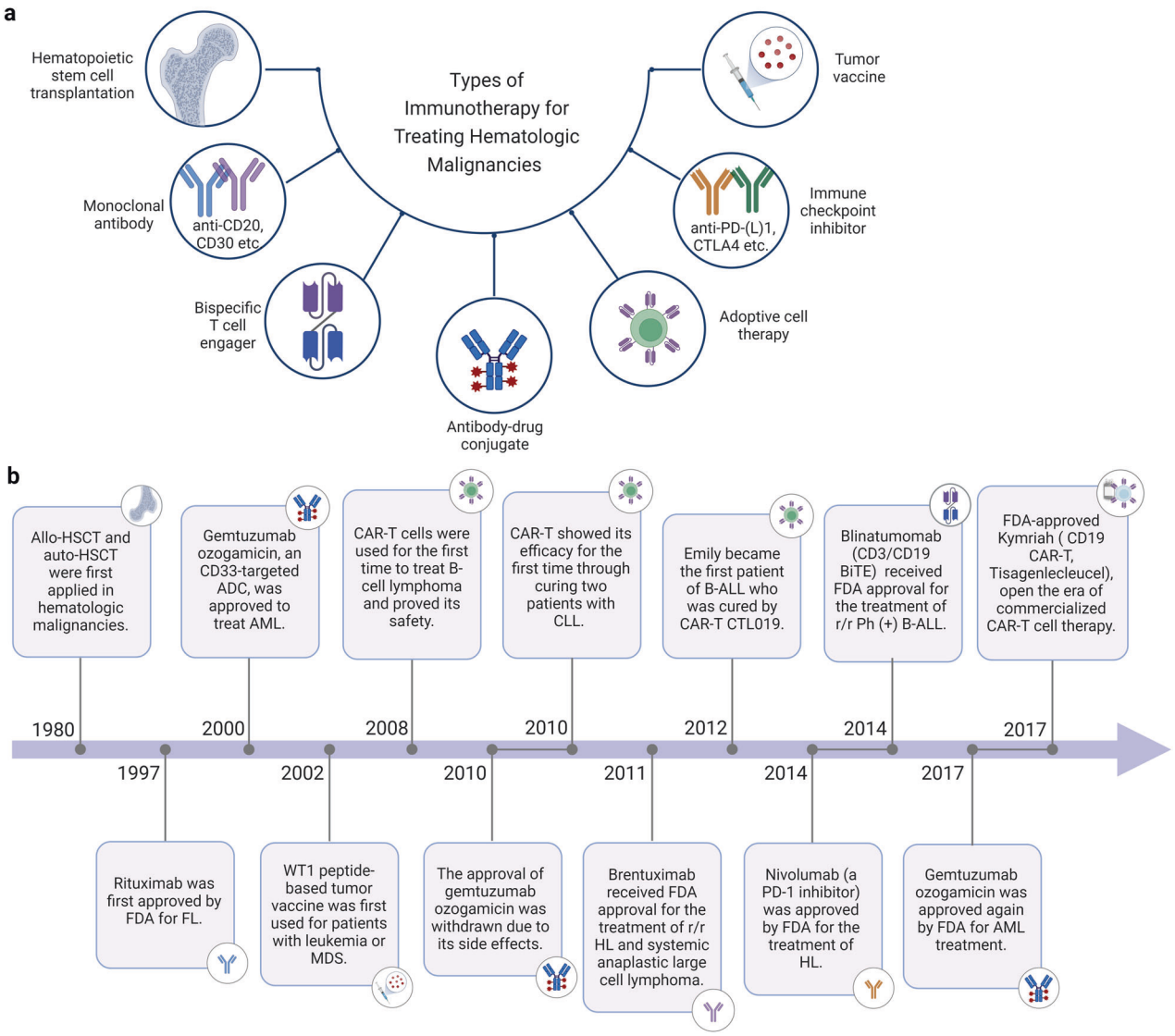

Fig. 1 The development of immunotherapy for hematologic malignancies. **a** Types of immunotherapies for treating hematologic malignancies. **b** The journey of the history of immunotherapy for hematologic malignancies

and mortality and can be performed in a wider range of patients.[42,43] Meanwhile, cord blood transplantation with a low relapse rate and chronic GVHD was also promoted but was later hampered by a high incidence of infection and transplant-related mortality. However, the safety and feasibility of HSCT using single UM171-expanded cord blood were validated in patients with malignant hematologic diseases who did not have a suitable HLA (human leukocyte antigen)-matched donor, indicating the potential to overcome the disadvantages of other cord blood transplantation while maintaining the benefits of low risk of chronic GVHD and relapse.[44] Haploidentical family donors, such as parents, children, or haploidentical siblings, offer the advantage of rapid donor availability. Currently, two methods are most commonly used for haploidentical hematopoietic stem cell transplantation (haplo-HSCT): (i) granulocyte colony-stimulating factor (G-CSF) plus anti-thymocyte globulin-based regimen with non-manipulated T-cell enriched grafts, which was originated by the Peking group in China; (ii) post-transplantation cyclophosphamide-based regimens with non-manipulated T-cell enriched grafts, which was initiated by the Baltimore group in the United States.[35,45–47] With the development of haplo-HSCT, strategies to address the associated side effects have become a research trend. A substantial improvement in non-relapse mortality and supportive care (e.g., treatment and prevention of infections or GVHD) has contributed to improved OS of allogeneic transplantation over the past decades.[48,49] In addition, to overcome barriers such as donor availability, novel transplantation strategies have been refined. For example, post-transplant cyclophosphamide for GVHD prevention after haploidentical donor transplants has shown similar outcomes with a reduced risk of GVHD.[50,51] The recurrence of the malignancy remains the most prevalent cause of post-transplant failure or even death, emphasizing the importance of enhancing the immune system in the treatment of hematologic malignancies and how far we have yet to go to achieve a cure. Although much is still being discovered, we have learned a great deal about how the host immune system affects the treatment of hematologic malignancies from the growing and evolving field of allogeneic transplantation, which is helping to advance the field of novel immunotherapies.[20]

mAbs

The mAbs are highly homogeneous IgG antibodies produced from a single B cell clone and directed against only specific antigenic

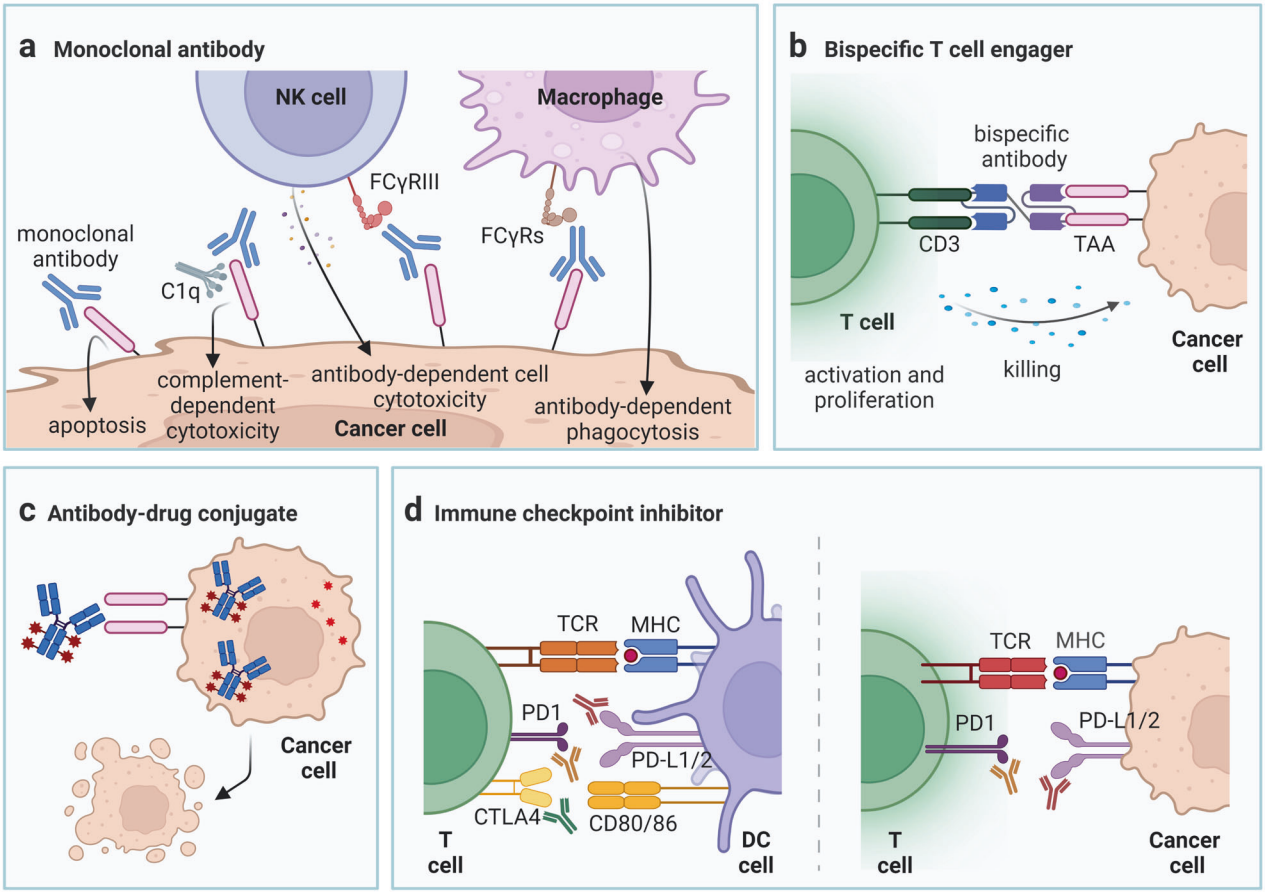

Fig. 2 Mechanisms of action of four kinds of immunotherapy drugs. **a** The monoclonal antibodies (mAbs), when combined with their targets, can kill cancer cells by direct induction of apoptosis through programmed cell death, antibody-dependent cell cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent macrophage-mediated phagocytosis. **b** The BiTE ((bispecific T cell engager) molecule usually targets one CD3 molecule and one tumor antigen simultaneously. Thus, in addition to the anti-cancer role of the tumor antigen-targeted antibody, it can promote the activation and recruitment of CD3 + T cells. **c** After bound to the tumor surface antigen, the antigen undergoes endocytosis and the antibody-drug conjugates (ADCs) will be internalized into the tumor cell and subsequently transported to the lysosome to release the cytotoxic payload, which can induce apoptosis and kill surrounding cancer cells through bystander effects. **d** The blockade of PD-1 or its ligands PD-L1 and PD-L2 can help to restore the anti-tumor immunity of the body and simultaneously enhance the lysis effect of cytotoxic T cells to achieve the effect of tumor eradication. CTLA-4 inhibitors can block the binding between CTLA-4 molecule and B7 during T cell activation, increase the level of the recognition of T cells to tumor-associated antigens (TAAs) and enhance the anti-tumor responses of the body's immune effector cells

epitopes. The first-generation mAbs are derived from mice and typically prepared using the hybridoma technique, which is based on cell fusion technology that fuses sensitized murine B cells with the capacity to secrete specific antibodies and myeloma cells with the capacity to multiply indefinitely into B cell hybrids.[52] Through culturing individual hybridoma cells with such properties into cell populations, it is possible to generate antibodies against corresponding antigenic epitopes. However, murine mAbs can be recognized by the immune system and result in human anti-mouse antibody reactions, particularly human anti-mouse antibody (HAMA),[53–55] resulting in limited efficacy of mAbs and potentially serious AEs. Since then, mAbs have gradually evolved toward the trend of humanization. The second generation is human/mouse chimeric mAbs (with the suffix -ximab, e.g., rituximab),[21] using chimeric antibody or humanized modified monoclonal antibody technology.[56,57] Both approaches greatly reduce the human anti-mouse immune response, but a certain degree of immunogenicity still exists because they contain mouse-derived sequence fragments. The subsequent mAbs are fully humanized (with the suffix -zumab and -mumab), with the amino acid sequences that make up the antibodies all derived from humans. These mAbs are mainly manufactured by phage display screening,[58,59] yeast surface display,[60,61] human hybridoma technology and single B-cell antibody preparation technology,[62] or even metabolic strategy like glycoengineering.[63] Meanwhile, these mAbs have a 100 percent human component and reduced immunogenicity, although they may still have immunogenicity due to anti-idiotype antibodies.

The mAbs are the major component of cancer immunotherapy.[64] mAbs have various mechanisms of action and each type of antibody has multiple mechanisms of action in parallel, mobilizing multiple aspects and components of immunity to ultimately kill tumor cells. The mAbs, when combined with their targets, can kill cancer cells in two ways (Fig. 2a): (i) direct induction of apoptosis through programmed cell death (PCD);[65] (ii) immune-mediated mechanisms, mainly including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and antibody-dependent macrophage-mediated phagocytosis due to the binding of Fc and FcγR (Fc gamma receptor).[65–70]

Rituximab is a first-generation anti-CD20 mAb. Ofatumumab is one kind of second-generation, fully-humanized anti-CD20 mAb that binds to a different site from rituximab and was approved by the FDA for the treatment of CLL in 2009, as well as in combination with chlorambucil for the treatment of CLL in

Table 1. Representative antibody-based drugs used for treating hematologic malignancies

Type	Drug	Target	Indication	If FDA approved?	Refs.
mAbs	Rituximab	CD20	B-NHL	Yes	85–88
	Ofatumumab	CD20	CLL	Yes	90
	Obinutuzumab	CD20	DLBCL, MCL, FL, CLL	Yes	74,92–95
	Ibritumomab tiuxetan	CD20	B-NHL	Yes	89
	Veltuzumab	CD20	B-NHL, CLL	No	91
	Ocrelizumab	CD20	FL	No	96
	Ocaratuzumab	CD20	B-NHL, CLL	No	97–99
	Ublituximab	CD20	CLL	No	354
	Epratuzumab	CD22	B-NHL	No	114
	Tafasitamab	CD19	DLBCL, FL	Yes	23,352
	Inelituzumab	CD19	B-NHL	No	112
	Galiximab	CD80	FL	No	113
	Alemtuzumab	CD52	PTCL, CLL	Yes	100,101
	MDX-060	CD30	HL, ALCL, T-NHL	No	102,103
	Daratumumab	CD38	MM	Yes	75–78
	Isatuximab	CD38	MM	Yes	82–84
	Dacetuzumab	CD40	MM, NHL, DLBCL	No	104–106
	Elotuzumab	CS1 (SLAMF7)	MM	Yes	79–81
	Milatuzumab	CD74	MM, MCL, FL, CLL	Yes	107–110
	Lintuzumab	CD33	AML	No	25
	BI 836858	CD33	AML	No	111
bsAbs	Blinatumomab	CD19/CD3	B-ALL, B-NHL, DLBCL	Yes	124–126
	AFM11	CD19/CD3	B-ALL	No	127
	Mosunetuzumab	CD20/CD3	FL	Yes	131
	Glofitamab	CD20/CD3	B-NHL, DLBCL	No	132,133
	Epcoritamab	CD20/CD3	B-NHL, DLBCL/LBCL, FL	No	134,135
	Odronextamab	CD20/CD3	B-NHL, DLBCL	No	136
	Plamotamab	CD20/CD3	B-NHL, DLBCL	No	137,138
	Teclistamab	BCMA/CD3	MM	Yes	150–154
	Linvoseltamab	BCMA/CD3	MM	No	155,156
	Elranatamab	BCMA/CD3	MM	No	157,158
	Alnuctamab	BCMA/CD3	MM	No	159
	AMG420	BCMA/CD3	MM	No	162
	TNB-383B	BCMA/CD3	MM	No	163
	AMG701	BCMA/CD3	MM	No	164
	PF-06863135	BCMA/CD3	MM	No	165
	Bi38-3	CD38/CD3	MM	No	160
	AMG424	CD38/CD3	MM	No	161
	ISB-1342	CD38/CD3	MM	No	166
	GBR-1342	CD38/CD3	MM	No	167
	Talquetamab	GPRC5D/CD3	MM	No	168
	Cevostamab	FcRH5/CD3	MM	No	169
	Flotetuzumab	CD123/CD3	AML/MDS	No	142,146
	XmAb14045	CD123/CD3	AML	No	147
	AMG330	CD33/CD3	AML	No	143
	AMV564	CD33/CD3	AML/MDS	No	144
	JNJ-63709178	CD33/CD3	AML	No	145
	MCLA117	CLEC12A/CD3	AML	No	148
	ESK1-BiTE	WT1/CD3	AML	No	149
	AFM26	BCMA/CD16A	MM	No	175
	TandAb	CD30/CD16A	HL	No	176
	CS1-NKG2D biAb	CS1/NKG2D	MM	No	178

Table 1. continued

Type	Drug	Target	Indication	If FDA approved?	Refs.
tsAbs	TsAb	CD19/CD22/CD3	B-ALL	No	177
	161533 TriKE	CD16/IL-15/CD33	AML	No	179
CiTE	CiTE	PD-L1/CD33/CD3	AML	No	613
SMITE	SMITE	CD19/CD3 & CD28/PD-L1	CD19-positive lymphoma or leukemia	No	614
ADC	Inotuzumab ozogamicin	CD22	B-NHL, B-ALL	Yes	187,188
	Moxetumomab pasudotox	CD22	HCL, B-ALL	Yes	189,190
	Pinatuzumab vedotin	CD22	DLBCL, FL	No	191
	BL22	CD22	B-ALL, HL	No	192,193
	Polatuzumab vedotin	CD79b	B-NHL, DLBCL, FL	Yes	191,209,210
	Loncastuximab tesirine	CD19	B-NHL, DLBCL	Yes	203,204
	Coltuximab ravtansine	CD19	B-ALL, B-NHL	No	205,206
	Denintuzumab mafodotin	CD19	B-ALL	No	207
	Combotox	CD19 and CD22	B-ALL	No	208
	Naratuximab emtansine	CD37	B-NHL	No	213
	AGS67E	CD37	B-NHL, T-NHL, CLL, AML	No	214,215
	Brentuximab vedotin	CD30	cHL, PTCL, ALCL, CTCL	Yes	181,194–197
	Camidanlumab tesirine	CD25	cHL	No	221
	Belantamab mafodotin	BCMA	MM	Yes	211
	HDP-101	BCMA	MM	No	212
	Indatuximab ravtansine	CD138	MM	No	216
	Lorvotuzumab mertansine	CD56	MM	No	217
	Milatuzumab doxorubicin	CD74	MM	No	218
	LM-305	GPRC5D	MM	No	219
	Gemtuzumab ozogamicin	CD33	AML	Yes	198
	Vadastuximab talirine	CD33	AML	No	199,200
	IMGN779	CD33	AML	No	201,202
	Pivekimab sunirine	CD123	AML	No	220

mAbs monoclonal antibodies, *bsAbs* bispecific antibodies, *tsAb* trispecific antibodies, *CiTE* bifunctional checkpoint inhibitory T cell–engager, *SMITE* Simultaneous multiple interaction bispecific T-cell engager, *ADC* antibody-drug conjugate, *FDA* Food and Drug Administration, *B-NHL* B-cell non-Hodgkin lymphoma, *DLBCL* diffused large B-cell lymphoma, *FL* follicular lymphoma, *MCL* mantle cell lymphoma, *CLL* chronic lymphocytic leukemia, *cHL* classical Hodgkin lymphoma, *ALCL* anaplastic large cell lymphoma, *PTCL* peripheral T-cell lymphoma, *MM* multiple myeloma, *AML* acute myelocytic leukemia, *B-ALL* B-cell acute lymphoblastic leukemia, *MDS* myelodysplastic syndromes, *HCL* hairy cell leukemia, *CTCL* cutaneous T-cell lymphoma, *BCMA* B cell maturation antigen, *GPRC5D* G protein-coupled receptor, *FcRH5* Fc receptor homolog 5, *CLEC12A* C-type lectin domain family 12 member A, *NKG2D* natural killer cell group 2 member D

2014.[71,72] Obinutuzumab is another second-generation anti-CD20 mAb and was approved by the FDA in combination with chlorambucil for the treatment of CLL in 2013 and in combination with bendamustine for the treatment of R/R FL in 2016.[73,74] Daratumumab is an anti-CD38 mAb that was FDA-approved for the treatment for patients with MM.[24] Elotuzumab is an anti-CS1 mAb that was approved by FDA in combination with lenalidomide and dexamethasone for the treatment of R/R MM in November 2015.[20] Furthermore, the FDA-approved mAbs, such as daratumumab,[75–78] elotuzumab,[79–81] and isatuximab,[82–84] have already revolutionized the standard of care for treatment of MM, or even in the front-line therapeutic setting. Up to now, as presented in Table 1, many kinds of mAbs have been developed for the treatment of hematologic malignancies with their targets involving CD20, CD19, CD22, CD38, CS1 (SLAMF7), CD52, CD40, CD80, CD74, and CD33.[25,74–114]

bsAbs

In complex disease pathogenesis, multiple mediators facilitate the stimulation of different signaling pathways or promote overlapping signaling cascades, which limits the therapeutic efficacy of the targeting of a single molecule.[115] Therefore, the bsAbs, which combine the binding sites of two mAbs in the same molecule, were developed and transformed into immunotherapy.[116] The emerging bsAbs, exemplified by BiTEs, which promote the activation and recruitment of CD3 + T cells, have facilitated the fast development of cancer immunotherapy in hematologic malignancies.[117–120] Similar as mAbs, the targeted antigens of bsAbs must be selected from tumor-associated antigens (TAAs) with high specificity and high correlation with the malignant phenotype of the tumor.[120,121] The bsAbs are mainly divided into three categories according to their targets: (i) antibodies that target two different tumor antigens; (ii) antibodies that target one tumor antigen and one immune-related molecule, such as CD3 for BiTE; and (iii) antibodies that target two immune-related molecules.[117] Because the BiTE molecule usually targets one CD3 molecule and one tumor antigen simultaneously, it belongs to the second category of bsAbs (Fig. 2b).[117] BiTEs are the main patterns by which bsAbs work in hematologic malignancies, such as blinatumomab (anti-CD19/CD3 bsAb) approved by the FDA for R/R ALL,[26,122–126] AFM11 for B-ALL,[127] anti-CD19/CD3 or anti-CD20/CD3 bsAbs for B-NHL,[128–138] anti-CD33/CD3, CD123/CD3, WT1/CD3, or CLEC12A (C-type lectin domain family 12 member A)/CD3 bsAbs for AML or MDS,[139–149] and anti-BCMA (B cell maturation antigen)/CD3 or CD38/CD3 bsAbs for MM.[150–167] In addition, the anti-GPRC5D (G protein-coupled receptor, family C, group 5, member D)/CD3 and anti-FcRH5 (Fc

receptor homolog 5)/CD3 bsAbs were also used for the treatment of MM.[168,169] Table 1 presents the bsAbs currently developed for hematologic malignancies. Although BiTEs have been proven to be efficient in many R/R hematologic malignancies, several patients still show no responsiveness to BiTE therapy. It is not only due to defects in the structure itself but also the immune escape, involving the aspects of loss of target antigen expression, disrupted trafficking of the target antigens and extramedullary lesions.[170–174] Based on this fact, bsAbs and trispecific antibodies (tsAbs) engaging NK cells have also been explored in pre-clinical and/or clinical studies.[175–179] Ross et al. reported the NK-cell mediated lysis of BCMA-positive MM cell lines induced by AFM26 (anti-BCMA/CD16A bsAb).[175] Moreover, the anti-CD19/CD22/CD3 tsAb that site-specifically fuses anti-CD19 scFv (single chain variable fragment) and anti-CD22 nanobody to CD3 antigen-binding fragment, was designed for treating patients with B-ALL.[177] It demonstrated enhanced anti-tumor efficacy and the capacity to overcome immune evasion when compared with the corresponding bsAbs alone or multiple antibodies in combination.[177] The therapeutic effects provide a new direction for the development of bispecific and even multi-specific antibodies.

ADCs

The mAbs have the advantage of a longer plasma half-life, yet they are not inherently cytotoxic. In contrast, small molecule cytotoxic agents commonly utilized in chemotherapy have high cytotoxicity and relatively low costs of production, but they are poorly targeted to cancer cells and have a plasma half-life of only a few hours.[180–182] The concept of utilizing the specific binding properties of mAbs as a mechanism to selectively deliver cytotoxic agents to tumor cells is an appealing approach to overcome the challenges of increasing the therapeutic potentials of cytotoxic agents. All three components of an ADC, the antibody, cytotoxic payload, and the linker chemistry that joins them together, are important for the design of an effective anticancer agent. Mechanistically, ADC differs from the previously mentioned mAb and bsAb in that after it binds to the tumor surface antigen, the antigen undergoes endocytosis and ADC will be internalized into the tumor cell and subsequently transported to the lysosome to release the cytotoxic payload (Fig. 2c). The released toxic payload can induce apoptosis and kill surrounding cancer cells through bystander effects (Fig. 2c).[183] Perhaps the most essential aspect of developing an effective molecule is the selection of the targeted antigen to which the ADC will bind.[184–186] Advances in related technology, improvements in the selection of cytotoxic agents and the use of smaller conjugates have all dramatically enhanced the potential clinical benefits of ADCs. Several ADCs have been designed and used for clinical use in hematologic malignancies and their targets include CD22,[187–193] CD30,[181,194–197] CD33,[198–202] CD19,[203–208] CD79,[191,209,210] BCMA,[211,212] CD37,[213–215] CD138,[216] CD56,[217] CD74,[218] GPRC5D,[219] CD123,[220] and CD25,[221] (Table 1). The initial excitement for ADCs has risen and then fallen with the approval and subsequent withdrawal of gemtuzumab ozogamicin in the years 2000 and 2010, respectively.[20] With effectiveness in the treatment of R/R HL and SALCL, brentuximab vedotin, an anti-CD30 antibody linked to a microtubule inhibitor monomethyl auristatin E (MMAE), received FDA approval for cancer treatment in 2011 and for post-autologous HSCT consolidation in 2015.[196,222] Inotuzumab ozogamicin is comprised of a humanized anti-CD22 mAb conjugated to calicheamicin, a cytotoxic antibiotic agent and was as monotherapy for the treatment of CD22-positive B-ALL in 2017.[180,223,224] Vadastuximab talirine (SGN-CD33A, 33A), a novel ADC consisting of pyrrolobenzodiazepine dimers linked to a mAb targeting CD33, has demonstrated activity and a tolerable safety profile as a single agent in patients with AML.[199] Belantamab mafodotin[225] targeting BCMA is currently the only ADC approved by the FDA for MM. Furthermore, other TAAs expressed highly on MM cells are also designed as targets of ADCs. Clinical trials of lorvotuzumab mertansine (anti-CD56 ADC),[217] indatuximab ravtansine (anti-CD138 ADC),[216] milatuzumab doxorubicin (anti-CD74 ADC),[218] and the first anti-GPRC5D ADC, LM-305,[219] are ongoing in present.

ICIs

Although more ICIs have been developed already,[226,227] anti-CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab, pidilizumab) and PD-L1 antibodies (atezolizumab, avelumab and durvalumab) have been the focus of current clinical consideration of checkpoint inhibitors.[32] PD-1 is a prominent immunosuppressive transmembrane molecule that is expressed on the surface of T cells.[228] In the tumor microenvironment (TME), T cells express high levels of PD-1 molecules, which can bind to PD-L1 on tumor cells or other immune cells and PD-L2 on macrophages and dendritic cells (DCs). This will inhibit the intracellular signaling transduction of T cells, reduce effector T cell activity, induce T cell apoptosis, negatively regulate the anti-tumor immune response and ultimately cause tumor cells to undergo immune escape.[229–233] In addition to surface PD-L1 molecule, tumors can also secrete soluble PD-L1, which more readily binds to PD-1 on T cells.[234,235] Furthermore, immune cells in TME sometimes are accomplices as well. Despite the direct suppression of T cells, Treg-expressed CTLA-4 can deplete CD80/CD86 by trogocytosis to release free PD-L1 on antigen-presenting cells.[236] Presence of PD-L1-expressing DCs and macrophages in TME may play a dominant role in mediating T-cell immunosuppression.[234] The use of mAbs or inhibitors targeting PD-1 or its ligands PD-L1 and PD-L2 can selectively block PD-1 and ligand binding between tumor cells and T cells, thereby helping to restore the anti-tumor immunity of the body and simultaneously enhance the lysis effect of cytotoxic T cells to achieve the effect of tumor eradication (Fig. 2d).[237] Once the "Cancer-Immunity Cycle" is established, it can produce long-lasting anti-tumor effects. PD-1 inhibitors also enhance the efficacy through the activation of other immune cells within the TME.[238] A robust anti-tumor T-cell response is induced in tumor-draining lymph nodes by blocking PD-L1-mediated inhibition of host antigen-presenting cells (APCs) at off-tumor sites.[239] A further opinion has been recently expressed that the activity of ICI is not limited to TME. PD-1 blockade drives the expansion of a subset of PD-1^{low}CD8+ progenitor cells with self-renewal properties, resulting in the mobilization of stem-like precursor CD8 + T cells that reside outside the tumor.[240] CTLA-4 molecule is normally expressed on the surface of CD4+ and CD8 + T cells and can bind with high affinity to B7 ligands on APCs, producing signals that inhibit T cell activation, reduce cytokine production and decrease the anti-tumor immune response.[241,242] CTLA-4 inhibitors block the co-stimulatory signal between CTLA-4 molecule and Fc on the surface of regulatory T cells, which can induce regulatory T cell death; in addition, this can also block the binding between CTLA-4 molecule and B7 during T cell activation, increase the level of T cell recognition to TAAs and enhance the anti-tumor responses of the immune cells (Fig. 2d).[243–245] T cell dysfunction, the metabolic profile of CD8 + T cells and immunosuppressive factors lead to resistance of ICIs.[246–249] The use of PD-1 blockade can also induce anti-PD-1 resistance by induction of dysfunctional PD-1+CD38^{high}CD8+ cells.[250] Therefore, combination therapy of ICIs is emerging in the treatment of hematologic malignancies.[251–253]

ACTs

ACT is a kind of immunotherapy in which autologous or allogeneic immune effector cells, activated and expanded in vitro, are infused into the patient. Such therapies are divided into non-specific and specific cellular therapies. Non-specific cellular therapy includes the direct infusion of cytokine-induced killer (CIK) cells, tumor-infiltrating lymphocytes (TIL), γ/δ T cells and NK cells, some of which have been used for hematologic malignancies.[254–258] The mechanism by which non-specific cellular therapy alleviates tumor symptoms is to boost the immunity of the entire body, leading to limited efficacy. Therefore, specific cellular therapies, particularly

CAR-T cells, have become more popular in clinical studies.[259,260] An incredible area of immunotherapy for hematologic malignancies is the development and refinement of CAR-T cell therapy. Such therapies involve not only targeting tumor antigens but also augmenting these targeted immune effectors. CAR-T cells are designed to express CAR that aims to target specific tumor surface antigens with antigen specificity and HLA independence and is therefore not dependent on MHC (major histocompatibility complex) expression. CAR-NK cells, not only recognize tumor antigens specifically via the CAR but also eliminate tumors by the NK cell receptor itself. NK cell activity depends on the balance of stimulatory and inhibitory signals and is antigen non-specific. Targeted lysis of CAR-NK cells is based on CAR-dependent and NK receptor-dependent mechanisms and this lysis effect is also indicated for antigen-negative cancer cells.[34,261,262] The main sources of CAR-NK cells are usually peripheral blood, cord blood, induced pluripotent stem cells (iPSCs) and NK92 cell lines. Since CAR-T therapy has the largest number of clinical trials and the widest range of applications in the field of cell therapy in hematologic malignancies, especially for multi-line therapy-refractory patients, we will focus on CAR-T therapy in the following sections.

The design of the CAR is the pivotal issue and has undergone several updates throughout the evolution of CAR-T therapy (Fig. 3a). Eshhar et al. were the first to construct the CAR-T cells for the expression of antigen receptors.[263] The intracellular structural domain of first-generation CAR-T cells contains only the signal transduction structural domain CD3-ζ, so that CAR-T cells have poor proliferative abilities and a short survival time in vivo, due to the absence of co-stimulatory signaling and cytokine signaling, such as interleukin-2 (IL-2).[264,265] The co-stimulatory structural domain CD28 or 4-1BB (also known as CD137) were integrated with the CD3-ζ molecule in the design of the second-generation CAR-T cells, which allowed CAR-T cells to continuously proliferate and induce enhanced anti-tumor activity.[266,267] The second-generation CAR-T cells, which are the most widely used in clinical practice, were able to exert anti-tumor effects even in the absence of exogenous costimulatory molecules.[268] Two different costimulatory domains (CD28/4-1BB or ICOS/4-1BB) are present in third-generation CAR-T cells.[269–271] The fourth-generation CAR-T cells incorporate cytokines or co-stimulatory ligands to further enhance T-cell responses, or suicide genes to enable CAR-T cells to self-destruct when needed.[272,273] The fifth-generation CAR-T cell is also derived from the second-generation and includes a shortened cytoplasmic IL-2 receptor β chain domain (IL-2Rβ) and a STAT3 binding moiety.[274] This design enables the fifth-generation CAR-T cells to enhance the T cell receptor (TCR) and cytokine-driven JAK-STAT signaling pathways to promote the proliferation and activation of the bioengineered T cells.[274] In addition to improvements through co-stimulatory domains and cytokines, more important is the design of the antigen-binding region scFv of CARs. The earliest scFv targeting CD19 was also of murine origin (FMC63) and it would generate murine-derived mAbs, namely anti-CAR immune responses. Moreover, this response has also been shown to affect CAR-T efficacy and even lead to late relapse.[275,276] Therefore, researchers are continuously working on humanizing scFv fragments and directly design fully human CAR fragments to reduce the occurrence of this response and its impact on efficacy.[277–279] Besides, more novel types of CAR-T cells are being developed to improve the flexibility of CAR target recognition. To address the problem of wait for a long time, the "off-the-shelf" CAR-T cells, in which all T cells are derived from healthy donors, have been developed.[280,281] The universal CAR-T cells replace scFv extracellular structural domain used in previous generations of CAR T cells with an adapter-specific recognition structural domain which binds to an adaptor molecule specific to a tumor target. This design enables CAR-T cells to recognize multiple antigens by separating the antigen-targeting structural domain from the T-cell signaling unit.

CAR-T cell therapy is a multi-step process that involves selecting eligible patients, collecting cells, manufacturing CAR-T cells, lymphodepletion, infusion of CAR-T cells, and subsequent longitudinal follow-up (Fig. 3b). The eligibility of patients depends on their disease status, previous treatment regimens, risk factors, comorbidities, performance status and social factors.[282] The patient's peripheral blood mononuclear cells (PBMCs) are collected by leukapheresis and CD3 + T cells are further purified and isolated. T cell subpopulations are genetically modified to express the CAR of interest, then expanded in vitro. The expanded CAR T cells are frozen and stored for future use and ultimately reinfused into the patients after lymphodepletion-directed chemotherapy. CAR T-cell therapy generally requires hospitalization and the patient's physical reactions, especially the possibility of AEs, should be closely monitored for several weeks after infusion.

CAR-T cell immunotherapy has gradually become the main therapeutic option for malignant hematological diseases, with impressive results to date. From Kymriah and Yescarta, which were the first to be approved by the FDA for the treatment of leukemia and lymphoma in August and October 2017, respectively, to the latest advances such as CB-010 therapy, they all play a pivotal role in treating malignancies, especially in cases of R/R patients. CAR-T cell immunotherapy has already achieved notable successes in the treatment of B-cell malignancies such as ALL, CLL, and DLBCL. Meanwhile, the most commonly utilized CAR targets for B-cell malignancies are CD19, CD20, and CD22.[283] Of these, CD19 is the most commonly used target and is highly expressed in the majority of B-cell malignancies. CD7 is an important target in T-cell ALL and T-cell lymphoma.[284–286] CD30 is usually expressed on tumor cells of HL,[287] and CD33 is a favorable target for AML.[288] Two CAR T-cell products, idecabtagene vicleucel and ciltacabtagene autoleucel, are the currently FDA-approved BCMA-targeting therapies. In addition to BCMA, many other investigational CAR T-cell therapies for MM are being studied, including cell products targeting SLAMF7, CD19, CD38, TACI (transmembrane activator and CAML interactor), GPRC5D (G protein-coupled receptor, class C, group 5, member D), and CD138.[282,289–291] However, the application of CAR-T therapy has been limited by relapse, resistance and toxicity.[292–298] Researchers have used diverse approaches to improve CAR-T therapy. In terms of target selection, new targets have been diligently searched for,[299,300] and even dual-target and even multi-antigen-targeted CAR-T have been introduced[291,301–306] to prevent subpopulations of tumors from being ignored.[307] For T-ALL, patients' own T cells are difficult to make CAR-T, thus healthy donor T cells are used to prepare CAR-T.[281] Recently CAR-NK and CAR-macrophage cells have also become new popular products and novel CARs are designed to overcome treatment failure.[308–310] Despite these advancements in CAR-T cell therapy, there are still several unanswered questions. For example, the optimal CAR T cell design and engrafting technique, the ideal intracellular costimulatory domain or the generation of CARs, the appropriate CD4:CD8 T cell ratio in infusion products and even factors such as the dominance of effector versus central memory cells and the influence of Tregs are unknown. The best timing for the engraftment of CAR-T cells is also not yet clear and may vary depending on the type of malignancies. In addition, the impact of TME may be an additional critical factor in CAR T-cell therapy. Although these questions remain unanswered, CAR T-cell therapy will be an essential strategy for the treatment of hematologic malignancies. As more research is conducted on this breakthrough therapeutic approach, it will be improved in its efficacy and applicability.

Tumor vaccines

Tumor vaccines, one of the hot topics in research in recent years, are immunotherapeutic modalities in which tumor antigens are infused into patients in various forms to generate tumor-specific lymphocytes in the patient and kill the tumor.[311] It consists of

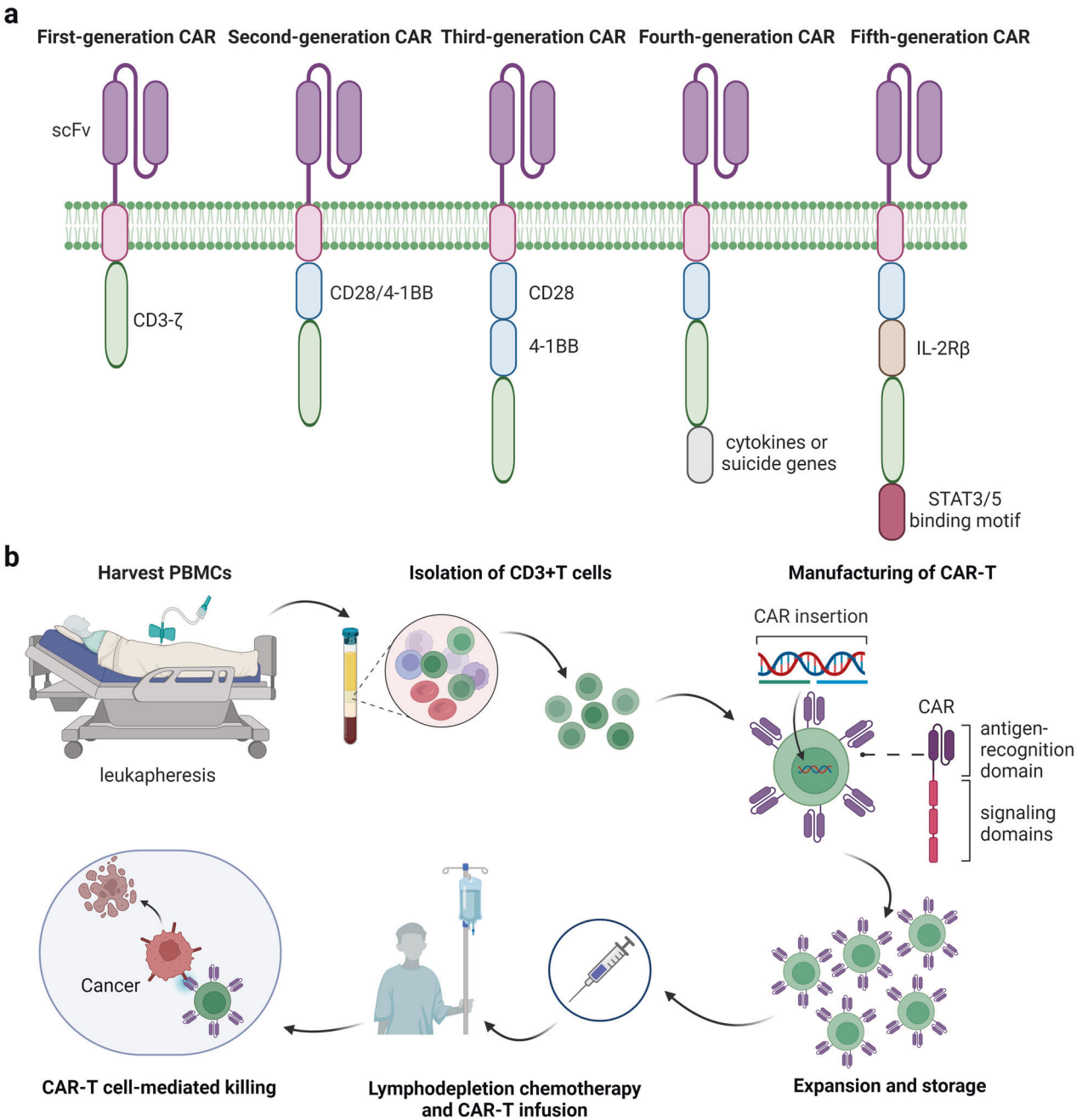

Fig. 3 The evolution of CAR design and the process of CAR-T therapy in clinic. **a** The design of the CAR has undergone several updates throughout the evolution of CAR-T therapy. To date, there have been five generations of CAR structures. **b** CAR-T cell therapy is a multi-step process that involves selecting eligible patients, collecting cells, manufacturing CAR-T cells, lymphodepletion and infusion of CAR-T cells and subsequent longitudinal follow-up

molecular vaccines and cellular vaccines, among which molecular vaccines include tumor-associated proteins or peptides and gene vaccines expressing tumor antigens. Cellular vaccines, on the other hand, are tumor cells, which are genetically modified to express MHC molecules and then injected into patients. Tumor vaccines can enhance the immunogenicity of the tumor, activate the patient's immune system, induce the body's cellular and humoral immune response and also override the immunosuppressive state caused by the tumor. It is designed to not only induce tumor regression, but also to eliminate minimal residual disease (MRD), establish long-lasting anti-tumor memory and avoid non-specific or adverse reactions. Such vaccines have been developed for B-cell leukemia and lymphoma, ranging from commonly-mutated genes to DC vaccines.[312,313] Vaccines targeting immunoglobulin light chain and EBV antigens are also available.[314,315] As clinical trials have been conducted,[316–318] although not yet widely used, the prospects are promising.

HOW IMMUNOTHERAPIES WORK: TO PROMOTE "CANCER-IMMUNITY CYCLE"

The generation of anti-cancer immunity is a cyclical process that can be self-perpetuating, with the accumulated immunostimulatory factors that should, in principle, boost the T cell immune response. This cycle can also be interrupted by suppressive stimuli, which result in immunomodulatory feedback mechanisms that

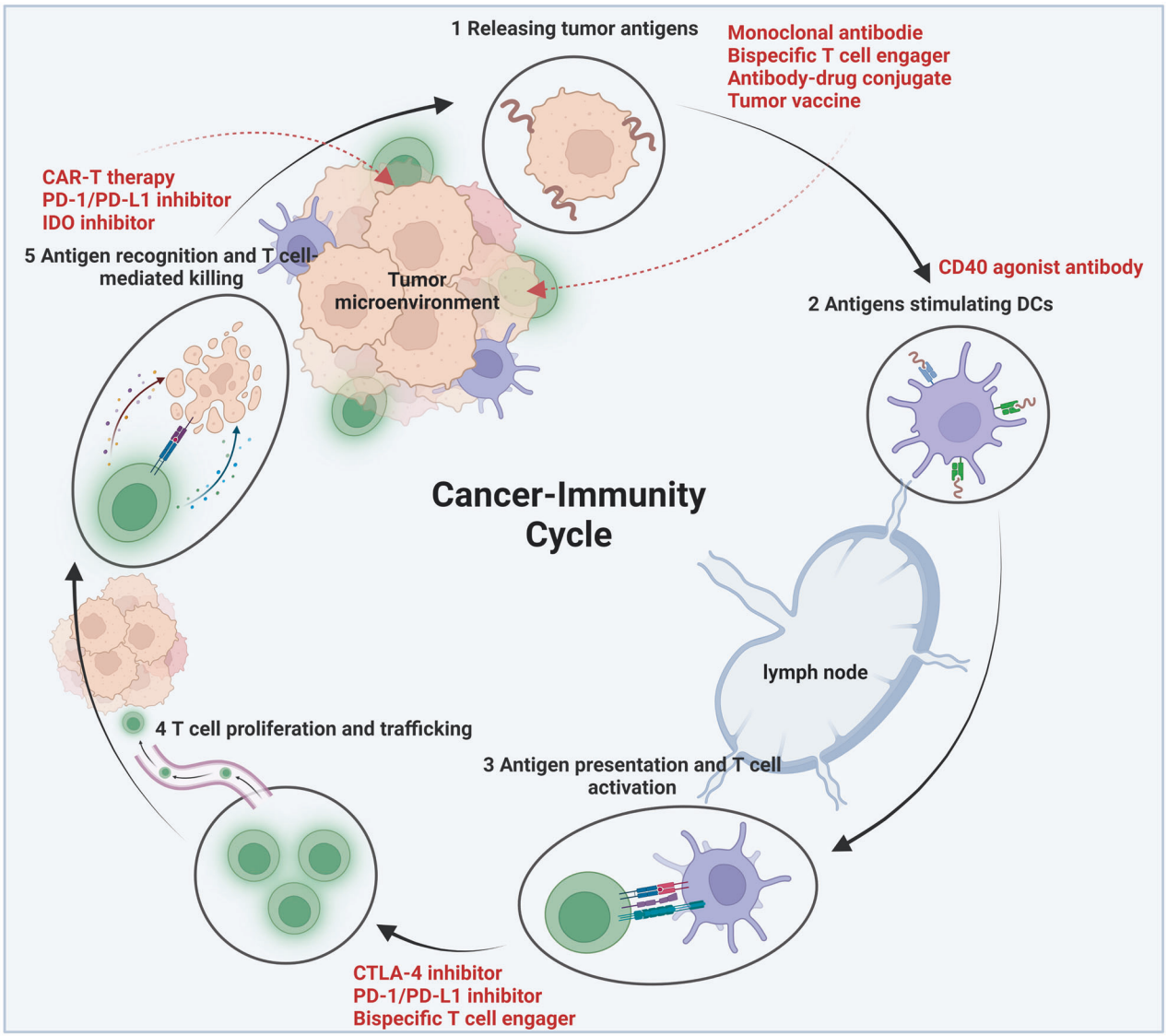

Fig. 4 How immunotherapies work? To promote "Cancer-Immunity Cycle". The "Cancer-Immunity Cycle" can be divided into multiple steps.[6] Dysregulation of the "Cancer-Immunity Cycle" is the consequence of tumorigenesis and treatment failure. Meanwhile, the TME may also suppress these effector cells engaged in the "Cancer-Immunity Cycle" and resultant cancer immune evasion. Numerous factors that play a part in any step of this cycle offer a wide range of potential therapeutic targets: (i) promoting antigen release, presentation and recognition; (ii) priming and activating the immune response; (iii) overcoming immune evasion; (iv) targeting immune suppression in the TME

impede the generation of anti-cancer immunity.[6] Generally, the "Cancer-Immunity Cycle" can be divided into multiple steps. First, the neoantigens that are produced during tumorigenesis are released and then captured by the DCs for processing. This must be accompanied by immune-specific signals so as not to induce peripheral immune tolerance to the tumor antigens. Then, DCs deliver antigens that are captured on MHC molecules to T cells, leading to the priming and activation of effector T cells. Subsequently, through the interaction between the TCR and the cognate antigen bound to MHC-I, these activated effector T cells traffic towards and infiltrate into the tumor, where they specifically recognize and bind to the cancer cells and kill them. Noteworthy, the killing of these targeted cancer cells also leads to the release of more TAAs. This in turn extends the breadth and depth of the immune response in subsequent cycles of rotation.[6] Dysregulation of the "Cancer-Immunity Cycle" is the consequence of tumorigenesis and treatment failure. Meanwhile, the TME may also suppress these effector cells engaged in the "Cancer-Immunity Cycle" and resultant cancer immune evasion.[6,7] Therefore, cancer immunotherapy requires initiating and promoting the self-sustainability of the "Cancer-Immunity Cycle" so that it can normally amplify and spread, but not to the point of generating an unrestrained autoimmune inflammatory response. In the meantime, cancer immunotherapy also needs to be carefully tailored to counteract these negative feedback mechanisms.[8–10] Numerous factors that play a part in any step of the "Cancer-Immunity Cycle" offer a wide range of potential therapeutic targets (Fig. 4): (i) promoting antigen release, presentation and recognition; (ii) priming and activating the immune response; (iii) overcoming immune evasion; (iv) targeting immune suppression in the TME.

Promote antigen release, presentation and recognition

Although not established as immunotherapies, chemotherapy, radiotherapy and targeted therapies (e.g., mAbs, bsAbs, and ADCs) can kill large numbers of cancer cells, then promote antigen release and T cell activation. The majority of tumor vaccines are therapeutic vaccines, which are based on the principle that tumor antigens are introduced into the patient's body to improve

immunogenicity, activate the immune system and elicit cellular and humoral immune responses to control or eliminate the tumor.[311] Theoretically, it is feasible to promote the activation of the immune system through the specific proteins of cancer cells so as to eliminate cancer cells. Nevertheless, tumor antigens are heterogeneous thus the primary problem in tumor vaccine development is to find the universal or specific antigens expressed on the surface of tumor cells.[319,320] CD40 agonist antibodies are used to promote the maturation and antigen-presenting ability of DCs by mimicking CD40L cross-linking CD40, inducing the expansion of tumor antigen-specific cytotoxic T cells and thus eradicating tumors.[105,321,322] CAR T-cell therapy is the process of transferring genetic material with specific antigen recognition structural domain and T cell activation signal into T cells through genetic modification. In this way, the modified T cells can be activated in an MHC-independent manner by directly binding with specific tumor antigens and directly killing the tumor cells by releasing perforin, granzyme B, etc. and also by secreting cytokines to recruit human endogenous immune cells to help to kill tumor cells.

Priming and activation of immune response

CTLA-4, an inhibitory receptor that is expressed primarily on T cells, has a suppressive function on T cell activation and is upregulated upon T cell activation. Antibodies targeting the immunomodulatory receptor CTLA-4 have two putative mechanisms of action: direct inhibition of CLTA-4 binding to its cognate ligand and depletion of immunosuppressive regulatory T (Treg) cells via Fc-mediated immune-mediated mechanisms, mainly including ADCC and CDC.[245] More importantly, the BiTEs are able to redirect T cells to specific tumor antigens and to directly activate the T cells.[323] Because T cells lack Fcγ receptors, natural antibodies cannot directly recruit these T cells. The BiTE molecule typically targets a tumor antigen and a CD3 molecule at the same time. The CD3 molecule associates non-covalently with the T cell receptor (TCR) and participates in antigen-specific signal transduction that can induce T cell activation. In addition, directly expanding and making available increased numbers of functionally competent immune cells represents an intuitively desirable therapeutic concept.[19] HSCT refers to the transplantation of hematopoietic stem cells from a donor into a recipient to rebuild or restore the recipient's immune system. Cellular immunotherapy stimulates the body's anti-tumor immune response by isolating autologous or allogeneic immune effector cells, activating them in vitro and then injecting them into the body. As with CAR-T cell therapy, the scFv recognizes specific TAAs, including the proteins, glycoproteins and other components. CD3-ζ is typically a signaling region containing three ITAMs (immunoreceptor tyrosine-based activation motifs). Upon scFv recognition and binding to TAA, phosphorylation of the ITAM triggers ZAP70 signal transduction and subsequent signaling to initiate and prime the T cell immune responses.[324] This is a principle similar to antigen-antibody complementarity, which can bypass the MHC-dependent antigen presentation and enable the TAA to directly stimulate the activation of CAR-T cells.

Overcoming immune evasion

An important mechanism by which tumor immune evasion occurs is by suppressing the function of effector immune cells. Immune checkpoints are a class of molecules that have a negative effect on immune cell function and are most expressed in immune cells. They can regulate the degree of activation of the immune system, resulting in them playing an important role in the prevention of autoimmune effects. However, these molecules are susceptible to being hijacked by tumor cells, which means the tumor cells can bind to the corresponding ligand/receptor on the immune cell, activating the inhibitory pathway and preventing immune cells from killing the tumor, thus enabling the immune escape of the tumor.[3] ICIs aim to block the corresponding immune checkpoints to prevent the activation of the relevant immunosuppressive pathways and have been widely used in various types of solid and hematologic malignancies.[325,326] Moreover, T cell exhaustion occurs due to a multi-factorial etiology resulting from sustained exposure to tumor antigens, the loss of stimulation/secretion of effector cytokines, the involvement of immunosuppressive cell types and immunophenotypic alterations including increased expression of inhibitory receptors and checkpoints such as LAG3 (lymphocyte-activation gene 3), TIGIT (T cell immune receptor with Ig and ITIM domains), TIM3 (T cell immunoglobulin mucin 3). Therefore, T cell exhaustion may be reversed and the anti-tumor immune response enhanced by inhibitors targeting these inhibitory receptors and checkpoints.

Targeting immune suppression in TME

The TME is the internal environment in which tumor cells survive and develop and immune cells in the TME have different mechanisms of pro- or anti-tumor immune action in tumor growth and progression. Tregs suppress T cell activity either directly or by secreting suppressor cytokines such as IL-10 and TGF-β; myeloid-derived suppressor cells (MDSCs) suppress T cell activity and modulate the intrinsic immune response to suppress the immune response. Therefore, targeting the TME is another important mechanism of cancer immunotherapy. For example, overexpression of indoleamine 2,3-dioxygenase (IDO) in tumors inhibits T cell proliferation and promotes regulatory T cell differentiation and IDO inhibitors can effectively improve the immunosuppressive microenvironment of tumors and enhance the anti-tumor immune response.

REPRESENTATIVE CLINICAL TRIALS AND OUTCOMES

HSCT

Numerous clinical trials have validated the elimination of hematologic malignancies through transplantation.[327–329] Transplantation-related clinical trials mainly involve two aspects: (i) exploration of peripheral blood stem cell transplantation (PBSCT) and RIST; (ii) comparison of allogeneic HSCT with HLA genotype identical sibling donors (ISD) and haploidentical donors (HID). Around the beginning of the 21st century, several clinical trials were conducted to investigate the efficacy and safety of PBSCT.[330,331] These results confirmed the advantage of PBSCT in terms of hematopoietic system reconstitution. Meanwhile, it makes HSCT less harmful to the donor. To expand the application, RIST has been raised for those who can't tolerate allo-HSCT. And relevant clinical trials were designed to discover the appropriate chemotherapy regimen and compared RIST with high-dose conventional conditioning. A 7-year clinical trial showed that 8 out of 12 patients who received RIST were still alive after 1 year, while only 3 out of 13 patients who received high-dose chemotherapy were still alive.[332] Fludarabine-melphalan as a preparative regimen for RIST is associated with a significant reduction in transplant-related mortality according to an update from the MD Anderson Center.[333] The study in Europe has also shown a reduction in the non-relapse mortality rate in RIST.[334] To date, more clinical trials are ongoing to evaluate RIST in elderly patients with AML and MDS.[335–337] Haplo-HSCT is now being used regularly for patients. However, it was not until 2015 that the technology became more mature and clinical trials comparing it to the ISD-HSCT were conducted.[338,339] The results of haplo-HSCT performed in patients who were in remission did not differ significantly from those of ISD-HSCT. In later studies, both transplantation methods were applied to patients not in remission, where haplo-HSCT showed better efficacy.[340] Although there may be a higher rate of GVHD, it has the potential to be used in high-risk child patients.[341] In addition, haplo-HSCT can be followed by adoptive T-cell therapy and the results of such trials

have shown that T-cell infusion can be beneficial in reconstituting the immune system and preventing relapse.[342,343]

mAbs

The most representative mAb used in the treatment of lymphoma is none other than Rituximab. There is a pivotal phase II trial of rituximab monotherapy that was conducted in 166 patients with R/R low-grade NHL, in which the ORR was 48 and 6% of the patients achieved the complete response.[344] The stage was set for the approval of rituximab with these and subsequent results.[345] However, an increasing number of clinical trials have opted to use rituximab in combination with other chemotherapy regimens to improve efficacy. In 2001, one phase II trial of the first-line R-CHOP regimen was initiated in 33 patients with aggressive NHL. The results were surprising with an ORR of 94% and a CRR (complete response rate) of 61%, demonstrating for the first time the feasibility and safety of the R-CHOP regimen in these patients.[86] Clinical trials of R-CHOP in MCL were then conducted. As implied by the results of a prospective randomized trial conducted by the German Low-Grade Lymphoma Study Group (GLSG), R-CHOP was significantly superior to CHOP as first-line therapy in terms of ORR (94%), CRR (34%) and time to treatment failure (21 months), although no differences were observed in progression-free survival (PFS).[346] Currently, R-CHOP has been designated as the first-line treatment agent for NHL by the National Comprehensive Cancer Network (NCCN), while there are numerous clinical trials to validate the efficacy of R-CHOP as a treatment to overcome relapse or refractory of NHL.[347] It is approved in Europe and the United States for use in combination with chemotherapy to treat patients with previously untreated or R/R CLL.[348] For example, a phase II trial evaluated the efficacy of the addition of rituximab to first-line chemotherapy with fludarabine and cyclophosphamide. And the chemo-immunotherapy group achieved a better clinical outcome, with 65% of patients free of disease progression at 3 years after the randomization.[349] Venetoclax-rituximab was also proved to be able to be applied in R/R CLL with significantly higher rates of PFS(84.9%) at 2 years.[88]

The development of new mAbs is ongoing and clinical trials are being conducted. Ofatumumab, a fully human mAb, has been used as a single-agent CD20 immunotherapy in R/R CLL and FL in international clinical trials and has been shown to be an active, well-tolerated treatment with significant clinical improvements.[71,90,350] There are some clinical trials, such as GAUDI, GAUGUIN and GADOLIN, to investigate the efficacy of obinutuzumab (also called GA101) monotherapy and immunochemical combination with it in treating patients with DLBCL, MCL, FL and CLL.[73,92–95] It has also been used to treat CD20-positive indolent NHL refractory to rituximab. In this study, the median PFS was 25.8 months and OS was also prolonged, demonstrating the clinical benefit of obinutuzumab.[74,351] As well, tafasitamab (anti-CD19 mAb) is also approved for the treatment of R/R DLBCL and FL as a novel agent.[23,209,210,352,353] Some mAbs which has already been approved in autoimmune disease, such as alemtuzumab (anti-CD52 mAb) and ublituximab (anti-CD20 mAb), also expanded their indications to hematologic malignancies. In the GENUINE trial, ublituximab plus ibrutinib achieved encouraging efficacy in high-risk CLL and the ORR was 83%.[354] Alemtuzumab combined with CHOP similarly showed better outcomes with an ORR of 72% and CRR of 60% in the phase 3 trial.[100] In recent years, mAbs have gradually been introduced into the treatment of other hematologic malignancies. Daratumumab, an anti-CD38 mAb, is initially used as monotherapy in R/R MM. In a phase I-II dose-expansion study, daratumumab was administered to patients who had received a median of four prior therapies, including 76% of patients who had received autologous HSCT. The ORR was 36% in the cohort with a dose of 16 mg/kg and 10% in the cohort with a dose of 8 mg/kg. PFS was 5.6 months and 65% of patients who responded had no disease progression at 12 months.[76] The results of the SIRIUS trial were similar and both were favorable in terms of safety and exciting efficacy.[77] Daratumumab was also combined with classical regimens of MM to investigate the efficacy. The phase 3 trial suggested that the ORR was higher in the daratumumab combination group (82.9%) than that in the control group with bortezomib and dexamethasone alone (63.2%).[24] A similar outcome also occurred in the trial that compared the regimen of lenalidomide and dexamethasone, with an ORR of 92.9%.[75] Afterwards, daratumumab plus bortezomib, melphalan and prednisone was also considered as a prior-line therapy for untreated MM patients. And the outcome indicated that the addition of daratumumab resulted in a lower risk of disease progression or death.[78] Another anti-CD38 mAb named isatuximab has improved its effectiveness when combined with classical therapy regimens. Randomized phase 3 trials have been completed for all of thesecombinations.[82–84] Meanwhile, elotuzumab targeted CS1 on MM cells and also indicated encouraging results in serial clinical trials called ELOQUENT that was conducted in R/R and newly diagnosed MM patients.[80,81] In a word, mAbs occupy an important position in hematologic cancers and chemoimmunotherapy associated with mAbs has become a popular trend at the present.

bsAbs

In hematologic malignancies, bsAb therapy usually refers to the BiTEs. Blinatumomab is the first bsAb designed for this field. Some early clinical trials were conducted for NHL in the year 2008. Out of 38 patients who received blinatumomab, a response was only observed in 11 patients. And the longest duration of CR is 13 months in one MCL patient.[355] Furthermore, it has been studied in more cases of B-ALL. A phase II trial has demonstrated that blinatumomab is effective in MRD-positive B-ALL patients who are resistant to previous chemotherapy. The drug showed a high response rate, with an ORR of 76% and a relapse-free survival (RFS) rate of 78%.[356] Other studies showed similar results,[26,357,358] and blinatumomab is also effective in children and young adults with the first relapse of B-ALL.[359,360] Therefore, it has already become an approved therapy for R/R B-ALL. Recently, there're emerging trials to discover the efficacy of the combination therapies of blinatumomab and other regimens for newly diagnosed Philadelphia chromosome (Ph) positive or negative B-ALL.[124,361–363] Blinatumomab was also used to treat patients with R/R B-NHL and DLBCL and showed great anti-tumor efficacy.[125,126,364,365] Meanwhile, some novel bsAbs entered the market in 2022, representing the rapid development of this field. Mosunetuzumab, a CD20/CD3 bispecific antibody, was approved for R/R FL based on the results of the multicenter phase II study in which 90 patients with FL received mosunetuzumab and the ultimate CRR was 60%.[131] Glofitamab is also targeted to CD20 but has been shown to induce durable CR in patients with R/R DLBCL.[132,133] In the phase I/II study, 52 patients who had previously received CAR-T therapy were enrolled and 35% of them achieved a CR and 78% of CR were sustained at 12 months.[133] Epcoritamab, odronextamab and plamotamab are all anti-CD20/CD3 antibodies and relevant clinical trials have demonstrated that they are competitive in terms of efficacy and safety.[134,136] A anti-BCMA/CD3 bsAb, teclistamab, was the first BiTE developed for MM.[150–154] In the trial MajesTEC-1, teclistamab demonstrated promising efficacy, with durable responses that deepened over time and was well tolerated in R/R MM patients.[153] Another phase 1–2 study also showed that teclistamab resulted a high rate of deep and durable response in patients with triple-class-exposed R/R MM.[151] The ORR was 63%, the median duration of response was 18.4 months and the median duration of PFS was 11.3 months.[151] Patients enrolled in the trial MajesTEC-2 had received ≥1 prior line of therapy.[152] While in the trial s MajesTEC-4 and MajesTEC-7, newly-diagnosed patients were enrolled and teclistamab was combined with classical regimens for treating

MM.[150,154] In addition to teclistamab, other anti-BCMA/CD3 bsAbs have emerged currently, including linvoseltamab, elranatamab and alnuctamab and serial trials are being conducted.[155–159,366–368] In a Phase 2 study, 232 patients received talquetamab (anti- GPRC5D/CD3 bsAb) monotherapy and 70% of those experienced a response and the median duration of response was 10.2 months.[168] A multicenter, open-label, phase 1/2 study of flotetuzumab (MGD006, anti-CD123/CD3 bsAb) was conducted in 88 adults with R/R AML and showed acceptable safety and encouraging evidence of activity in PIF (primary induction failure)/ER (early relapse) patients.[142] JNJ-63709178, another kind of anti-CD123/CD3 bsAb, was found to have limited exposures and clinical activity with an unfavorable safety profile.[145]

ADCs

Over the past several decades, ADCs have been evaluated in many preclinical models and early-phase clinical trials of hematologic malignancies. Gemtuzumab ozogamicin, an anti-CD33 ADC, was once used in AML patients with their first relapse and no history of an antecedent hematologic disorder and a median age of 61 years. This was based on the result of the clinical trial which revealed that 30% of patients who were treated with gemtuzumab ozogamicin achieved a remission, characterized by 5% or fewer blasts in the bone marrow.[369] However, a phase III SWOG S0106 randomized comparative trial did not confirm the clinical benefit of gemtuzumab ozogamic in combination therapy, such as CR rate, disease-free survival (DFS) and OS. Moreover, increased toxicity was observed and probably caused by relatively high instability of the linker in the bloodstream combined with a high recommended dose.[370] Thus, gemtuzumab ozogamicin was withdrawn in 2010 due to its serious toxicities and poor outcomes of survival.[371–373] It has been re-approved until 2017, following adjustments to the dosage and conditions as well as extensive clinical trials.[374–377] At present, it is believed that the benefit of gemtuzumab ozogamicin can be predicted by some related conditions and this is the reason why gemtuzumab ozogamicin is used in AML with high CD33 expression levels and corresponding mutated genetic profiles (e.g. NPM-1 mutated, KMT2A rearranged).[198,378,379] Furthermore, gemtuzumab ozogamicin is effective when used in newly diagnosed core binding factor (CBF)-deficient AML in the clinical trial conducted by MD Anderson.[380] In addition, a humanized anti-CD22 ADC called inotuzumab ozogamicin was initially given to patients with R/R B-NHL in a phase 1 clinical trial. Unfortunately, the final ORR was only 39% for the 79 patients enrolled.[187] Later on, inotuzumab ozogamicin has been tried to be used in R/R B-ALL patients. In the phase 2 trial, the ORR was 57% for the 49 patients in the study.[381] To further demonstrate the promise of inotuzumab ozogamicin, it was compared to standard intensive chemotherapy for ALL in a phase 3 trial. In the inotuzumab ozogamicin group, the CR rate was significantly higher (80.7%), the median duration of remission was longer (4.6 months) and the median PFS was also longer (5.0 months).[180] Based on these results, the FDA approved the use of inotuzumab ozogamicin in adult R/R B-ALL. Meanwhile, clinical trials continued to evaluate the efficacy of the combination therapy in Ph(-) ALL and in pediatric patients.[188,382,383] Another anti-CD22 ADC, called moxetumomab pasudotox, has been developed for the treatment of R/R hairy cell leukemia (HCL).[189] In the long-term follow-up from the pivotal trial, complete responders lasting ≥60 months was 61% and median PFS without the loss of hematologic remission was 71.7 months. Moxetumomab pasudotox fills the gap in R/R HCL where there is no adequate therapy.[384] In 2022, brentuximab vedotin (anti-CD30 ADC) was used in patients with III/IV-stage cHL. Compared with the classical ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) regimen, the combination of brentuximab vedotin plus BVD (bleomycin, vinblastine and dacarbazine) showed better consequences with a 6-year OS of 93.9%.[181] Polatuzumab vedotin has been designed to target CD79b and used for the treatment of R/R B-NHL including DLBCL and FL.[191,209,210] Polatuzumab vedotin combined with bendamustine and rituximab resulted in a significantly higher CR rate and reduced the risk of death by 58% compared with bendamustine and rituximab in patients with transplantation-ineligible R/R DLBCL.[210] Loncastuximab tesirine (ADCT-402) is a humanized anti-CD19 IgG1 mAb conjugated through a protease-cleavable Val-Ala linker to a pyrrolobenzodiazepines dimer, a DNA crosslinking agent.[203,204] A phase 1 study of loncastuximab tesirine in R/R B-cell NHL showed that ORR in evaluable patients was 45.6%, including 26.7% CRs. ORRs in patients with DLBCL, MCL, and FL were 42.3%, 46.7%, and 78.6%, respectively.[185] Further, a multicentre, open-label, single-arm, phase 2 trial (LOTIS-2) was conducted in patients with R/R DLBCL after two or more multiagent systemic treatments with an ORR of 48.3% and a CRR of 24.1%.[203] Belantamab mafodotin chose BCMA as the target and fills the gap of ADC in MM and the serial trials continue to discover its clinical efficacy and durability as monotherapy or combined with other regimens.[211,385,386] The DREAMM-2, a two-arm, randomized, open-label, phase 2 study, demonstrated that 31% of 97 patients in the 2·5 mg/kg cohort and 34 of 99 patients in the 3–4 mg/kg cohort achieved an overall response.[211] In DREAMM-6 trial, belantamab mafodotin showed a better outcome with an ORR of 75% and a median PFS of 8.6 months.[386] It seems that ADCs have already played an important role and became a new trend in immunotherapy for hematologic malignancies nowadays. These ADC drugs have achieved satisfactory results in clinical trials and have been approved for use in the diseases for which they are intended.[191,203,204,210,353] Furthermore, there're still some novel ADCs waiting for approval and the corresponding clinical trials are ongoing.[199,200,221]

ICIs

Several clinical trials of ICIs have been conducted in hematologic malignancies, including MM, ALL, AML, NHL and HL.[387–390] However, only the results of PD-1 blockade in HL are particularly remarkable. Some observations may suggest why HL is uniquely sensitive to PD-1/PD-L1 blockade.[391] First, HL biopsies typically show the Reed-Sternberg (R-S) cells that are surrounded by an extensive immune infiltration, but it is ineffective. Moreover, increased surface expression of PD-L1 was also observed in HL biopsies. Second, HL is characterized by the genetic alterations in 9p24.1 that result in copy gain and overexpression of PD-L1 and PD-L2, with an increase in copy gain or amplification of 9p24.1 in more than 97% of newly diagnosed HL biopsy specimens.[392,393] Third, infection with Epstein-Barr virus (EBV) is common in HL patients and also causes PD-L1 to be overexpressed, which is one of the key mechanisms by which the virus could persist in the host.[394] In contrast, NHL does not display a high frequency of 9p24.1 alterations, thus the efficacy of ICI decreased for NHL patients.[395]

Table 2 gives a summary of representative clinical trials of ICIs that are already approved by the FDA or some novel ICIs (e.g., dual-target ICI) that are still in the stage of the clinical study.[387,396–407] Ipilimumab, a CTLA-4 inhibitor, has been evaluated in clinical trials of the treatment for NHL and HL patients,[396–398] but only showed certain therapeutic effects in HL with an ORR of 76% and CRR of 57%.[398] Since HL has the property of being more sensitive to ICIs targeting PD-1, most of the clinical trials of PD-1 blockades, including nivolumab, pembrolizumab and pidilizumab, were conducted on R/R HL.[194,387,396,398,400,408] In recent years, nivolumab and pembrolizumab have been used in patients with NHL, CLL[404,409,410] and even in some lymphomas for which there is no effective therapy, such as PCNSL (primary central nervous system lymphoma) and PMBCL (primary mediastinal large B-cell lymphoma).[402,403,411] Moreover,

Table 2. Representative clinical trials and outcomes of ICIs for treating hematologic malignancies

Drug & Target	Trial	Phase	Monotherapy/ combination therapy	Type of disease	Prior lines of treatment	No. of patients	Response	Survival	FDA approval	Refs.
Ipilimumab, CTLA-4	NCT00060372	I	Monotherapy	Pan-cancers, including R/R cHL	Received allo-HSCT	29	Only 3 patients demonstrated objective disease responses after ipilimumab alone, 1 patient achieved PR and 2 patients achieved CR	Median OS of all 29 patients was 24.7 months	Yes	[396]
	NCT00089076	I	Monotherapy	R/R B-NHL	1–4 chemotherapy regimens	18	Only 2 patients had clinical response: 1 patient achieved PR and 1 patient achieved CR	1 patient with FL had PR lasting 19 months and 1 patient with DLBCL had an ongoing CR (> 31 months)	Yes	[397]
	NCT01896999	I/II	Combination therapy	R/R cHL	≥1	61	ORR 76% CRR 57%	Median PFS 1.2 years	Yes	[398]
Ipilimumab and Nivolumab, CTLA-4 and PD-1	NCT01592370	I	Combination therapy	R/R cHL, NHL, and MM	≥1 or ≥2	65	cHL: ORR 74%, CRR 23% NHL: ORR 19%, CRR 6% MM: ORR 0%	cHL: median PFS was not reached at 17 months all corhorts: median PFS was 1–2 months	Yes	[399]
Nivolumab, PD-1	NCT01592370	I	Monotherapy	R/R cHL	≥1 without ASCT in 100 days	23	ORR 87% CRR 17%	PFS: 86% at 24 weeks; OS: 91% at 1 year	Yes	[387]
	NCT03016871	II	Comparison of monotherapy and combination therapy	R/R cHL	/	43	ORR 93% CRR 91%	PFS 72% at 2 years	Yes	[400]
	ADVL1412	I/II	Monotherapy	Pan-cancers, including NHL and HL	≥1	HL 10, NHL 10	HL: ORR 30% NHL: ORR 10%	HL: the median of cycles the patients completed was 4.5; NHL: one patient had response and remained on therapy for 11 cycles.	Yes	[401]
	/	/	Monotherapy	R/R PCNSL and PTL with CNS relapse	≥1	5	ORR 100% CRR 80%	PFS: 60% at 17 months	Yes	[402]
	CheckMate 436	I/II	Combination therapy	R/R PMBCL	≥2 or received ASCT	30	ORR 73% CRR 37%	Median PFS and OS were not reached	Yes	[403]
	NCT02038933	II	Monotherapy	R/R DLBCL	Experienced failure of ASCT	121	Allo-HSCT-failed: ORR 10% at 9 months, ASCT-ineligible: ORR 3% at 6 months	Allo-HSCT-failed: median PFS 1.9 months, median OS 12.2 months; allo-HSCT-ineligible: median PFS 1.4 months, OS 5.8 months	Yes	[404]
	NCT02329847	I/II	Combination therapy	R/R FL/DLBCL/ CLL and SLL/ RT	≥1	144	CLL/SLL: ORR 61% FL: ORR 33% DLBCL: ORR 36% RT: ORR 65%	CLL/SLL: median duration of response 19.2 months FL: median PFS 9.1 months DLBCL: median PFS 2.6 months RT: median PFS 5.0 months	Yes	[409]
Pembrolizumab, PD-1	KEYNOTE-013	I	Monotherapy	R/R cHL	Received BV without ASCT	21	ORR 65% CRR 16%	PFS 46% at 52 weeks	Yes	[408]
	KEYNOTE-013	I	Monotherapy	R/R PMBCL	Median 3	18	ORR 41%	Median OS was not reached	Yes	[411]
	NCT02453594	II	Monotherapy	R/R cHL	Received BV and/ or HSCT	210	ORR 69% CRR 22.4%	PFS 72.4%, OS 99.5% at 6 months	Yes	[405]

Table 2. continued

Drug & Target	Trial	Phase	Monotherapy/ combination therapy	Type of disease	Prior lines of treatment	No. of patients	Response	Survival	FDA approval	Refs.
	KEYNOTE-204	III	Monotherapy	R/R cHL	≥1 without ASCT	151	ORR 65.6%, CRR 24.5%	Median PFS was 13.2 months	Yes	194
	NCT02332980	II	Monotherapy	R/R CLL, RT	≥1	16	RT: ORR 44% CLL: ORR 0%	RT cohort: median OS 10.7 months	Yes	410
Pidilizumab (CT-011), PD-1	NCT00532259	II	Monotherapy	R/R DLBCL	Received ASCT	66	ORR 51%	PFS 72%, OS 85% at 16 months	Yes	390
	NCT00904722	II	Combination therapy	R/R FL	≥1	32	ORR 62%, CRR 52%	Median PFS was 18.8 months	Yes	406
	CT-011 Trial	I	Monotherapy	Advanced NHL, HL, CLL, MM	/	7	B-NHL: ORR 14%, CRR 14%	The survival time ranged from 1.7 to >77 weeks.	Yes	412
Margrolimab, CD47	NCT02953509	I	Combination therapy	DLBCL, FL	≥2	22	ORR 50%, CR 36%	91% of response were ongoing at median follow-up.	No	407
Lemzoparlimab, CD47	NCT03934814	I	Combination therapy	R/R NHL	≥2	8	ORR 57%, overall DCR 100%	All responders remained in clinical response at the time of data cutoff.	Yes	414
	NCT04202003	I	Monotherapy	R/R AML and MDS	≥2	5	1 patient achieved morphologic leukemia-free state	/	– n–	415
Evorpacept, SIRPα/ CD47	ASPEN-02	I/II	Combination therapy	R/R MDS	≥1 HMA-based regimen	13	ORR 60% of 5 ND patients, 40% of 5 R/R patients	/	Yes	417
TG-1081, CD19/CD47	NCT03804996	I	Comparison of monotherapy and combination therapy	R/R B-cell lymphoma	≥1	14	Monotherapy: ORR 21%; Combination with ublituximab: ORR 44%, CRR 6%	10 patients had durable response at the time of data cutoff.	No	413

FDA Food and Drug Administration, *R/R* refactory/relapse, *ND* newly diagnosed, *cHL* classical Hodgkin lymphoma, *ASCT* autologous stem cell transplantation, *ORR* overall response rate, *CR* complete response, *PFS* progression-free survival, *OS* overall survival, *DCR* disease control rate, *NHL* non-Hodgkin lymphoma, *PCNSL* primary central nervous system lymphoma, *CNS* central nervous system, *PTL* primary testicular lymphoma, *PMBCL* primary mediastinal large B-cell lymphoma, *DLBCL* diffused large B-cell lymphoma, *CLL* chronic lymphocytic leukemia, *BV* brentuximab vedotin, *RT* Richter transformation, *FL* follicular lymphoma, *MM* multiple myeloma, *AML* acute myelocytic leukemia, *MDS* myelodysplastic syndromes, *HMA* hypomethylating agents, "/", not available

there's a clinical trial of pidilizumab conducted in advanced hematologic malignancies including MM, promoting the wide application of ICIs.[412] In addition to PD-1 blockade, CD47 blockade has emerged as the treatment for R/R NHL, MM and especially for AML/MDS, where PD-1 blockade shows poor efficacy.[413–417] To improve the overall response, one phase 1b trial explored the safety and efficacy of combined PD-1 and CTLA-4 blockade in patients with R/R lymphoid malignancies, including HL, NHL, and MM.[399] But it is regrettable that there was no meaningful improvement in the efficacy of the combinations over single-agent nivolumab in the diseases studied. While this combination was active in HL (ORR 74%, CRR 23%), the toxicity of nivolumab /ipilimumab was higher than expected from nivolumab alone.

ACTs

Our primary focus has been on the large clinical trials of CAR-T cell therapy in various hematologic malignancies. Table 3 gives a summary of representative clinical trials and outcomes of CAR-T cell monotherapy for blood cancers. Tisagenlecleucel, axicabtagene ciloleucel and lisocabtagene maraleuecel are the most representative anti-CD19 CAR-T cell products and they have been studied in a large number of clinical trials. For tisagenlecleucel, ELIANA has indicated its efficacy in pediatric patients with B-ALL.[418] Other clinical trials with tisagenlecleucel are predominantly focused on B-NHL. Among them, JULIET investigated the CAR-T therapeutic efficacy in R/R DLBCL,[419] BELINDA raised tisagenlecleucel as second-line treatment,[420] and ELARA enrolled patients with R/R FL.[421] The clinical trials for axicabtagene ciloleucel are called ZUMA[422–427] and cover the treatment of R/R LBCL, B-ALL, and MZL. The most recent one, ZUMA-12, demonstrated the high response rate of axicabtagene ciloleucel as first-line therapy for untreated high-risk LBCL.[427] Lisocabtagene maraleuecel has fewer trials in comparison with the two products above, but the 2022 TRANSCEND CLL 004 study showed surprising results suggesting an ORR of 82% in patients with R/R CLL and small lymphocytic lymphoma (SLL).[428] However, the antigen expression of tumor cells still limits the efficacy of CAR-T therapy. Since CD19 may not cover all types of lymphoma subclones,[428–430] CAR-T cells targeting other highly-specific antigens and dual targets,[302,431–437] such as CD22, CD19/CD20, and CD30, have been developed as well. The anti-CD30 CAR-T cells have also been developed in HL,[435–437] and more clinical trials are being conducted to verify their efficacy.

In addition to lymphoma and leukemia, CAR-T cells have also made great progress in treatment of MM.[278,438–446] Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) have already been approved by the FDA based on responses and safety demonstrated in the KarMMa and CARTITUDE-1 trials.[439,440,442] Meanwhile, more companies have launched CAR-T cell products for MM, such as orva-cel, P-BCMA-101.[443,444,446–449] CAR-T cell products against the new target, GPRC5D, have also been developed without delay. Usually, patients enrolled in CAR-T clinical trials have a good baseline condition. This is to prevent them from not being able to tolerate side effects such as CRS. However, the first clinical trial of the GPRC5D target was conducted in patients with poor baseline conditions who had received multiple lines of therapy.[299] The clinical results also showed a high level of safety and efficacy, taking the development of CAR-T to a new level. In other types of hematological malignancies, CAR-T therapy is still in the exploratory phase of development. A single-center, single-arm, phase 2 trial assessed the activity and safety of a combination of humanized anti-CD19 and anti-BCMA CAR T cells in patients with R/R MM and confirmed that this combined infusion is feasible with ORR of 95% and CRR of 43%.[450] As for AML, CAR-T therapy seems to be less effective due to the lack of appropriate tumor targets and is still being explored in preclinical and clinical studies.[289,451–453] The difficulty of manufacturing cell products using autologous T cells is the major problem facing CAR-T therapy in T-ALL. As a result, several institutions have developed donor-derived CAR-T cells and have conducted clinical trials to confirm the efficacy and safety of these CAR-T cells.[281,284,454] The donor-derived CAR-T cells suggested encouraging effects, especially in those patients who received allo-HSCT.[455]

The universal CAR-T cells, also known as "off-the-shelf", can overcome the problem of long period of manufacturing and enable those patients whose T cells are under poor condition to receive CAR-T therapy. Due the heterologous nature of allogeneic CAR-T cells, many products are designed to knock out of the TCR or edit the CD52 gene to overcome GVHD and HVGD (host versus graft disease). It is slao essential to examine the safety and in vivo persistence of universal CAR-T cells through clinical trials.[446,456–460] Anti-CD19 universal CAR-T cells, like PBCAR0191 and bispecific universal CAR-T CTA101, also showed high rates of CR (60% and 83.3%).[301,461] 81.8% of patients showed OR after RD13-01 infusion (CRR 63.6%) without GVHD and severe CRS.[458] A phase 1 UNIVERSAL trial reported a first-in-class, allogeneic, anti-BCMA CAR-T cell therapy (ALLO-715) engineered to abrogate GVHD and minimize CAR-T rejection. ALLO-647 (anti-CD52 antibody) was used for lymphodepletion with fludarabine and/or cyclophosphamide before ALLO-715 infusion. There was obvious expansion in 83.3% of patients yet 63.3% of patients showed undetectable levels of CAR-T cells by the day 28.[446] Overall, universal CAR-T cells have made some progress, but the clinical safety, efficacy and the duration of response of these products still requires further observation.

Although CAR-T cell therapy has achieved outstanding results when used as a monotherapy, there are still certain patients who do not benefit from it and further research is urgently needed to improve and prolong the efficacy of CAR-T therapy. Therefore, researchers are focusing on the combination of other immunotherapies with CAR-T cell therapy. The immune checkpoint molecule PD-1 on the surface of CAR-T cells has been reported to be overexpressed due to T-cell overactivation and thus blocking the PD-1/PD-L1 pathway might effectively restore the function of CAR-T cells.[462] Clinical trials have been performed with the combination of PD-1 blockers and CAR-T therapy and the results have been encouraging. A phase II clinical trial of anti-CD30 CAR-T treatment in combination with PD-1 inhibitor in R/R CD30-positive lymphoma has been conducted. Among the 12 patients who were evaluated for response, the ORR was 91.7% and the CRR was 50%. And 7 patients maintained their response until the end of the follow-up.[463] Additionally, the combination of CD19 CAR-T cells and PD-1 blockade was proven to reduce intracranial tumor burden in a patient with centrally-invasive lymphoma.[464] However, some researchers have chosen to construct endogenous PD-1 dominant-negative receptors (DNRs) within CAR-T cells to allow them to bind both TAA and PD-1 on tumor cells, ensuring that CAR-T function is not inhibited.[465,466] In combination with CAR-T cell therapy, HSCT is also a popular alternative. Bridging therapy with donor CAR-T cells after allogeneic transplantation can have shown a prolonged effect on the efficacy of the transplant.[467,468] According to the results from a retrospective study, haplo-HSCT with pre-transplant negative MRD after CAR-T cell therapy can significantly improve LFS (leukemia-free survival) and OS in patients with R/R B-ALL.[469] This finding was confirmed in subsequent clinical trials. In the subgroups of patients who achieved MRD-negative CR after CAR-T cell therapy, event-free survival (EFS), and RFS were significantly prolonged by allo-HSCT.[470] As a result, CAR-T therapy followed by transplantation can improve survival in a similar manner and is a viable option for achieving a durable remission of the disease.

Currently, CAR-NK is also a hot topic of research, with the major advantage that NK cells are able to be produced from healthy donor-derived PBMC, core blood, or iPSCs (induced pluripotent stem cells) without any appreciable toxicity. 11 patients were

Table 3. Representative clinical trials and outcomes of CAR-T monotherapy for treating hematologic malignancies

Type of CAR-T therapy	CAR-T Product & Target	Structure of binding domain & costimulatory domain	Trial	Phase	Type of disease	No. of prior lines of treatment	No. of patients	Response	Survival	FDA approval	Refs.
Monospecific, autologous	Tisagenlecleucel, CD19	FMC63 scFv, 4-1BB	ELIANA	I/II	R/R B-ALL	1–8 (median 3)	75	ORR 81%, CR/CRi 81%	EFS 50%, OS 76% (12months)	Yes	[418]
			JULIET	II	R/R DLBCL	1–6 (median 3)	93	ORR 52%, CRR 40%	RFS 65%, OS 49% (12 months)	Yes	[419]
			BELINDA	III	Aggressive B-NHL	1	322	ORR 46.3%	PFS 25.9% (6 weeks)	Yes	[420]
			ELARA	II	R/R FL	2–13 (median 4)	97	ORR 86.2%, CRR 69.1%	PFS 67% (12 months)	Yes	[421]
	Axicabtagene ciloleucel (KTE- X19), CD19	FMC63 scFv, CD28	ZUMA-1	I/II	R/R LBCL	1–4 (median 3)	101	ORR 82%, CRR 58%	PFS 44% (12months), OS 52% (18 months)	Yes	[422]
	Brexucabtagene, CD19	FMC63 scFv, CD28	ZUMA-2	II	R/R MCL	1–5 (median 3)	71	ORR 93%, CRR 67%	PFS 61%, OS 83% (12months)	Yes	[423]
	Axicabtagene ciloleucel (KTE- X19), CD19	FMC63 scFv, CD28	ZUMA-3	I/II	R/R B-ALL	≥2 (median 2)	55	CR/CRi: 71%	Median RFS 11.6 months, median OS 18.2 months	–	[424]
			ZUMA-5	I/II	R/R FL or MZL	2–3 (median 3)	153	ORR 96%, CRR 77%	PFS 74%, OS 93% (12 months)	–	[425]
			ZUMA-7	III	R/R LBCL	1	179	ORR 83%, CRR 65%	EFS 41% (24 months)	–	[426]
			ZUMA-12	I/II	High-risk LBCL	Untreated	40	ORR 89%, CRR 78%	PFS 75%, OS 91% (12 months)	Yes	[427]
	PD1-19bbz, CD19	Anti-CD19 scFv, 4-1BB	NCT04213469	I	R/R B-NHL	Not treated with CAR-T	8	ORR 100%, CRR 87.5%	PFS 100% (12 months)	No	[465]
	Lisocabtagene maraleuecel, CD19	FMC63 scFv, 4-1BB	TRANSCEND NHL001	I	R/R LBCL	1–4 (median 3)	269	ORR 73%, CRR 53%	Median follow-up for OS 18.8 months	Yes	[267]
			TRANSFORM	III	R/R LBCL	1	92	ORR 79%, CRR 61%	PFS 52.3%, OS 79.1% (12 months)	Yes	[429]
			PILOT	II	R/R LBCL	1 (without HSCT)	61	ORR 49%, CRR 33%	Median PFS 9.03 months	Yes	[430]
			TRANSCEND CLL 004	I	R/R CLL/SLL	≥2 (median 4)	23	ORR 82%, CRR 45%	Median PFS 18 months	Yes	[428]
	CD20 CAR-T	/	ChiCTR2000036350	I	R/R B-NHL	1	15	ORR 100%, CRR 80%	PFS and OS 100% (12.4 months)	No	[431]
	CD22 CAR-T	Anti-CD22 scFv, 4-1BB	NCT02315612	I	R/R B-ALL	≥1 (except 1 untreated)	21	CRR 57%	Among the 12 patients who attained CR, 3 remain in ongoing CR at 21, 9 and 6 months. 8 patients relapsed 1.5–12 months post CAR infusion.	No	[432]
Monospecific, universal (allogenic)	ALLO-501A, CD19	Anti-CD19 scFv, with disrupted TCRα and edited CD52 gene	ALPHA2	I/II	R/R LBCL	≥2	15	ORR and CR 50%	/	No	[456]
	CTX110, CD19	Anti-CD19 scFv, with disrupted TCR and elimination of β_2-microglobulin gene	CARBON	I	R/R LBCL	≥2	32	ORR 67%, CRR 41%	Nearly 50% patients received CR maintained it out to at least 6 months	No	[459]
	PBCAR0191, CD19	Anti-CD19 scFv, with TCR/CD3 knockout	NCT03666000	I/II	R/R B-ALL	≥2	15	CR/CRi 60%	One patient achieved progression-free more than 250 days. Others had progression or died less than 150 days.	No	[461]
					R/R B-NHL	≥2	13	ORR 77%, CRR 54%	Duration of response assessment is ongoing.	No	[460]
	UCART22, CD22	anti-CD22 scFv,4-1BB	BALLI-01	I	R/R B-ALL	≥1	9	CRi 11%	/	No	[457]

Table 3. continued

Type of CAR-T therapy	CAR-T Product & Target	Structure of binding domain & costimulatory domain	Trial	Phase	Type of disease	No. of prior lines of treatment	No. of patients	Response	Survival	FDA approval	Refs.
Bispecific, autologous	CD19/22-CAR T	Anti-CD19 FMC63 scFv and anti-CD22 m971 scFv, 4-1BB	NCT03233854	I	R/R B-ALL/ LBCL	≥2	38	B-ALL: ORR 100%, CRR 88%; LBCL: ORR 62%, CRR 29%	B-ALL: median OS 11.8 months, median PFS 5.8 months LBCL: median OS 22.5 months, median PFS 3.2 months	No	433
	LV20.19, CD19/20	Anti-CD19 FMC63 scFv and anti-CD20 leu-16 scFv, 4-1BB	NCT03019055	I	R/R B-NHL, CLL	2–12 (median 4)	22	ORR 82%, CRR 64%	Median OS 20.3 months	No	434
	TanCAR7 T cells, CD19/ CD20	Anti-CD19 FMC63 scFv and anti-CD20 leu-16 scFv, 4-1BB	NCT03097770	I/II	R/R B-NHL	≥1 (most are 3–5)	28	ORR 79%, CRR 71%	PFS 64% (12 months)	No	302
Bispecific, universal (allogenic)	CTA101, CD19/CD22	Anti-CD19 FMC63 and anti-CD22 m971 scFv with CRISPR/Cas9-disrupted TCRα region and CD52 gene, 4-1BB	NCT04227015	I	R/R B-ALL	≥1	6	CR/CRi 83.3%	50% patients remained MRD negative at a median follow-up of 4.3 months	No	301
Monospecific, autologous	CD30.CAR-Ts, CD30	Anti-CD30 scFv derived from HSR3 antibody, 4-1BB	NCT02690545 NCT02917083	II	R/R HL	2–23 (median 7)	41	ORR 62%, CRR 51%	PFS 36%, OS 94% (1 year)	No	435
	CD30.CAR-Ts, CD30		NCT01316146	I	R/R HL/ALCL	≥3	9	ORR 33.3%	HL; 1 patient remained CR for 2.5 years, 1 patient remained CR for 2 years ALCL: 1 patient remained CR for 9 months	No	436
	CART-30, CD30		NCT02259556	I	R/R HL	≥10	18	ORR 39%	Median PFS 6 months	No	437
Monospecific, autologous	Idecabtagene vicleucel (ide-cel, bb2121), BCMA	Murine anti-BCMA scFv, 4-1BB	NCT02658929	I	R/R MM	3–23 (median 7)	33	ORR 85%, CRR 45%	Median PFS 11.8 months	Yes	438
			KarMMa	II	R/R MM	3–16 (median 6)	128	ORR 73%, CRR 33%	Median PFS 8.8 months	Yes	439
			KarMMa	III	R/R MM	2–4	254	ORR 71%, CRR 39%	Median PFS 13.3 months	Yes	440
	bb21217, BCMA		CRB-402	I	R/R MM	3–17 (median 6)	69	ORR 60%, CRR 28%	Median PFS was not reached	No	441
	Ciltacabtagene autoleucel, BCMA	Llama- derived anti-BCMA VHH, 4-1BB	CARTITUDE-1	I/II	R/R MM	4–8 (median 6)	97	ORR 97%, sCR 67%	PFS 77%, OS 89% (12 months)	Yes	442
	CT103A, BCMA	Fully human anti-BCMA scFv, 4-1BB	ChiCTR1800018137	I	R/R MM	3–6 (median 4)	18	ORR 100%, sCR/CR 72.2%	PFS 58.3% (12 months)	No	278
	P-BCMA-101, BCMA	Murine anti-BCMA scFv, 4-1BB	PRIME	I/II	R/R MM	2–18 (median 8)	53	ORR 57%	/	No	443
	Orva-cel, BCMA	Humanized anti-BCMA scFv, 4-1BB	EVOLVE	I/II	R/R MM	3–18 (median 6)	62	ORR 92%, CRR 36%	/	No	444
	CT053, BCMA	Humanized anti-BCMA scFv, 4-1BB	Lummicar-2	I/II	R/R MM	2–11 (median 4)	14	ORR 100%, sCR/CR 40%	/	No	445
Monospecific, universal (allogenic)	ALLO-715, BCMA	Humanized anti-BCMA scFv with CD52 & TCR knockout, 4-1BB	UNIVERSAL	I	R/R MM	3–11 (median 5)	43	ORR 55.8%	Median DOR 8.3 months	No	446
Monospecific, autologous	MCARH109, GPRC5D	Humanized anti-GPRC5D scFv, 4-1BB	NCT04555551	I	R/R MM	4–14 (median 6)	17	ORR 71%, CRR 35%	PFS 50% (10.1 months)	No	299
	CC-95266, GPRC5D	Anti-GPRC5D scFv, 4-1BB	NCT04674813	I	R/R MM	≥3	17	ORR 89%, CR 47%	PFS 88% (at the time of analysis)	No	448
	OriCAR-017, GPRC5D	Anti-GPRC5D scFv with Ori, 4-1BB	POLARIS	I	R/R MM	≥3	10	ORR 100%, sCR 60%	PFS 80% (12months)	No	290

Table 3. continued

Type of CAR-T therapy	CAR-T Product & Target	Structure of binding domain & costimulatory domain	Trial	Phase	Type of disease	No. of prior lines of treatment	No. of patients	Response	Survival	FDA approval	Refs.
Combination of two monospecific CAR-T	CD19 and BCMA CAR-T	Humanized anti-CD19 scFv, murine anti-BCMA scFv, 4-1BB	ChiCTR-OIC-17011272	II	R/R MM	5–8 (median 6)	21	ORR 95%, sCR 43%, CR 14%	PFS 85% (602 days)	No	[450]
Bispecific, autologous	BM38, BCMA/CD38	Humanized anti-BCMA/CD38 scFv, 4-1BB	ChiCTR1800018143	I	R/R MM	2–9 (median 4)	23	ORR 87%, sCR/CR 54.5%	Median PFS 17.2 months	No	[291]
	BCMA/CS1	Murine anti-BCMA/CS1 scFv, 4-1BB	NCT04662099	I	R/R MM	≥2	16	ORR 100%, sCR 31%	OS 83.9%, PFS 55.2% (12 months)	No	[449]
Monospecific, HSCT donor-derived (allogenic)	CD7 CAR-T	Anti-CD7 scFv, 4-1BB	ChiCTR2000034762	I	R/R T-ALL	2–4 (median 3)	20	ORR 95%, CRR 90%	/	No	[284]
Monospecific, autologous	nanobody-derived fratricide-resistant CD7-CAR T	Humanized anti-CD7 nano- body-derived CAR, ICOS and 4-1BB	NCT04004637	I	R/R T-ALL/LBL	≥4	8	CRR 87.5%	/	No	[285]
Monospecific, autologous/donor-derived	NS7CAR, CD7	/	NCT04572308	I	R/R T-ALL/LBL	≥1	20	CRR 95%	/	No	[454]
Monospecific, universal (allogenic)	RD13-01, CD7	Anti-CD7 scFv with TCR/CD3 knockout and NK cell inhibitor, 4-1BB	NCT04538599	I	R/R T-ALL/LBL	2–7 (median 4)	12	ORR 81.8%, CRR 63.6%	/	No	[281]
Monospecific, autologous	CAR-T-38, CD38	Anti-CD38 scFv same as daratumumab, CD28 and 4-1BB	NCT04351022	I	R/R AML	>1 (received HSCT)	6	CR/CRi 66.7%	Median OS 7.9 months, LFS 6.4 months	No	[289]
	NKG2D CAR-T	Humanized NKG2D gene, without co-stimulation domain	NCT02203825	I	R/R AML/MDS/MM	0–4	12	ORR not seen	Median OS 4.7 months	No	[451]
	CLL-1 CAR-T	Anti-CLL-1 scFv, 4-1BB	ChiCTR2000041054	I	R/R AML	2–10 (median 5)	10	CR/CRi 70%	/	No	[452]
Monospecific, universal (allogenic)	UCART123v1.2, CD123	Anti-CD123 scFv, with disrupted TRAC and CD52 genes	Ameli-01	I	R/R AML	≥2 or received prior allogenic HSCT	8	ORR 25%	/	No	[453]

CAR-T chimeric antigen receptor T cell, *FDA* Food and Drug Administration, *scFv* single chain variable fragment, *R/R* relapsed or refractory, *B-ALL* B-cell acute lymphoblastic leukemia, *ORR* overall response rate, *CR* complete response, *CRi* complete remission with incomplete hematological recovery, *EFS* event-free survival, *OS* overall survival, *DLBCL* diffused large B-cell lymphoma, *RFS* relapse-free survival, *NHL* non-Hodgkin lymphoma, *PFS* progression-free survival, *FL* follicular lymphoma, *CRR* complete response rate, *LBCL* large B-cell lymphoma, *MCL* mantle cell lymphoma, *MRFS* median relapse-free survival, *MZL* marginal zone lymphoma, *HSCT* hematopoietic stem cell transplantation, *CLL* chronic lymphocytic leukemia, *SLL* small lymphocytic lymphoma, *HL* Hodgkin lymphoma, *ALCL* anaplastic large cell lymphoma, *MM* multiple myeloma, *sCR* stringent complete response, *DOR* duration of response, *T-ALL* T-cell acute lymphoblastic leukemia, *T-ALL/LBL* T-cell acute lymphoblastic leukemia/lymphoma, *AML* acute myelocytic leukemia, *LFS* leukemia-free survival, *MDS* myelodysplastic syndromes, *TRAC* T-cell receptor alpha constant, "/", not available

treated in a phase 1/2 study with anti-CD19 CAR-NK derived from core blood. Among them, 8 patients experienced a response and 7 of them experienced a CR. The infused CAR-NK cells proliferated and persisted in vivo at low levels for at least 12 months.[471] Although it was not effective in B-ALL patients unfortunately, NKX019 showed a favorable efficacy in R/R B-NHL patients and the ORR was 83% and CRR was 50% in the higher-dose group.[472] Besides, NKX101 targeted NKG2D (natural killer cell group 2 member D) and achieved an ORR of 47% in all R/R AML patients enrolled.[473] For R/R MM, FT576 was proved to be safe and tolerates without CRS, GVHD, or neurotoxicity and was determined a recommended dose in a phase 1 trial.[474] In addition, more researches on CAR-NK cells are still in the pre-clinical stage or early clinical trials.[308,475] Further research is also needed to perfect the design and manufacturing to improve the efficacy and durability of CAR-NK cells.[476,477]

AES AND TOXICITY MANAGEMENT

The era of immunotherapy has brought revolutionary breakthroughs for hematologic malignancies. These therapies are designed to stimulate the immune system to recognize and attack cancer cells, thereby extending survival and improving outcomes. However, immunotherapy poses new clinical problems and challenges for hematologists due to its toxicity, which is different from traditional chemotherapy, depending on the specific mechanism of action.[478] The occurrence of AEs cannot be ignored and can affect almost all organs and systems. These AEs further impede the clinical application of immunotherapy and, in severe cases, even threaten the patient's life.[478] Therefore, the need for and importance of toxicity management has become increasingly apparent. Treatment of AEs usually depends on the organ involved and the severity of symptoms. These toxicities often require specific management, including steroids and immunomodulatory therapy, for which consensus guidelines have been proposed and published. Here, we summarize the typical AEs associated with various immunotherapies, including HSCT, antibody-based therapies, ICIs, and CAR-T cell therapies, and then discuss their clinical management.

AEs of HSCT

Although HSCT can give some patients a chance at a cure, it is not an easy decision to be made. Transplantation has been a cure for thousands of patients with lethal forms of cancer. However, there can still be life-threatening risks and complications. Most of the side effects that can occur shortly after the transplant are the result of the bone marrow being destroyed by drugs or radiation just before the transplant. Others may be due to side effects of the conditioning treatments themselves. A short-term side effect that can occur with chemotherapy and radiation is mucositis. To prevent this, doctors often give anti-nausea medication at the same time as chemotherapy. Patients can easily get serious infections for at least the first six weeks after the transplant until the new stem cells start to produce white blood cells.[479–481] To prevent possible infections, antibiotics are used until the blood counts reach a certain level. It can take about 6 months to 1 year after the transplant for the immune system to take effect. Injuries and bleeding are other potential risk because the conditioning regimen can damage the body's ability to generate platelets. Pneumonitis is a type of inflammation of the lung tissue that's most commonly seen in the first 100 days after the transplant. However, some kinds of lung problems can occur much later after a transplant. Pneumonia caused by an infection is more common, but pneumonitis can also be caused by radiation, GVHD, or chemotherapy, rather than by the infection itself. Pneumonitis can be particularly severe if the patient has received total body irradiation with chemotherapy as part of the pre-transplant regimen. Acute kidney injury (AKI) directly related to stem cell transplant encompasses a wide range of both structural and functional disorders, which may be of the vascular (hypertension, thrombotic microangiopathy), glomerular (albuminuria, nephrotic glomerulopathies), and/or tubulointerstitial type.[482–484] AKI is a common complication following stem cell transplantation, affecting ~10–73% of patients.[482] A serious side effect in which tiny veins and other blood vessels in the liver become blocked is a hepatic veno-occlusive disease (VOD).[485] It is very rare and is only seen in people who have had an allogeneic transplant.[485,486] The onset of VOD is usually about 3 weeks after transplantation. It is more common in older patients who have had liver disease before the transplant and in patients who have acute GVHD. The symptoms are yellow skin and eyes, dark urine, tenderness under the rib cage and a rapid increase in body mass.[485] It is life-threatening, so it is very important to recognize and diagnose VOD at an early stage.[487,488]

GVHD. GVHD is a leading contributor to mortality and morbidity after allo-HSCT.[489,490] The donated immune cells may also attack some of the organs, most typically the skin, the gastrointestinal tract and the liver. As a result, there may be some changes in the functioning of the body's organs and an elevated risk of infections.[491] GVHD reactions are very common and can range in severity from barely noticeable to life-threatening.[39,492,493] Acute GVHD can occur between 10 and 90 days after the transplant and lasts for a short period of time. Chronic GVHD has a later onset and longer duration. The patient may experience one or both types of GVHD, or neither type of GVHD. Acute GVHD develops in approximately one-third to one-half of allogeneic transplant recipients. It is less frequent in the younger patients and the ones with a more closely matched HLA. A rash, burning and redness of the skin on the palms and the soles of the feet are usually the first symptoms. The rash may spread to the rest of the body. Other symptoms may include nausea, vomiting, stomach cramps, decreased appetite, jaundice, abdominal pain, and weight loss. Medications that can suppress the immune system may be given to prevent acute GVHD, such as steroids (glucocorticoids), methotrexate, cyclosporine, tacrolimus, or some types of mAbs.[492,494] These are administered before acute GVHD begins to occur. The risk of acute GVHD can also be reduced by the removal of immune cells from the donor stem cells prior to transplantation. However, this also increases the risk of viral infection, leukemic recurrence and graft failure. Researchers are exploring new ways to remove allo-activated T cells from donor transplants, which would reduce the severity of GVHD while still allowing donor T cells to destroy any remaining cancer cells. Mild cases of GVHD can usually be treated with topical steroid medications. More severe cases of GVHD may need to be treated with oral steroid medications or intravenous steroid medications. Chronic GVHD, which can lead to significant morbidity and mortality, usually occurs within one year of allo-HSCT.[495] When engrafted immune cells attack host cells, it causes inflammation and fibrosis in various types of tissues and multiple organ systems, such as the esophagus, gastrointestinal tract, neuromuscular system, genitourinary tract, liver, lungs, mouth, eyes, muscles, and joints.[495,496] Symptoms of chronic GVHD may include dry eyes, raised or discolored rash, thickened skin, swollen abdomen, yellowing of the skin and eyes, dry mouth, breathlessness, difficulty swallowing, fatigue, muscle weakness, and joint stiffness. Chronic GVHD can also be treated with immunosuppressive drugs, but these drugs increase the risk of infection. Most patients who have chronic GVHD will be able to stop taking the immunosuppressive medication if their symptoms are getting better.

Secondary cancers. It is possible for the original type of cancer to come back and for a second type of cancer to develop after the transplant.[497–499] The cancers that can develop are solid tumors in various organs, leukemia and MDS. They tend to occur a few years

or even longer after engraftment.[500,501] Post-transplant lymphoproliferative disorder (PTLD) is an out-of-control growth of lymphocytes that can occur following alloHSCT.[502,503] Normally, T cells assist the body in getting rid of virally infected cells. The pretransplant treatment compromises the immune system, enabling EBV infections to get out of control. PTLD after allo-HSCT is relatively rare and generally occurs within one to six months. The symptoms of PTLD consist of swollen lymph nodes, fever and chills.[503] Although there is no standard treatment, the usual management is to reduce the use of immunosuppressive drugs and encourage the patient's immune system to fight back. Other options involve infusing lymphocytes to boost the immune response and the administration of antiviral drugs.[503–506]

AEs of antibody-based therapies

Antibody-based drugs have been generally considered to be less toxic than cytotoxic chemotherapeutics used for cancer therapy, while some of these elements may be recognized as foreign substances and thereby cause hyperactivation of immune and innate reactions. A wide spectrum of AEs to antibodies is observed, necessitating efforts to identify, manage and minimize side effects. Some toxicities result from the binding of a therapeutic antibody to its target antigen on normal cells, which refers to the "on-target, off-tumor" toxicity. Therefore, the manifestations of such toxicities are dependent on the target of antibody drugs. For example, rituximab can cause profound first-dose toxicity related to the rapid lysis of normal and malignant B cells that bear the target antigen, CD20.[507] Acute reactions can be caused by a variety of mechanisms, including acute IgE-mediated hypersensitivity and anaphylactoid reactions against the antibodies, serum sickness, tumor lysis syndrome (TIS) and CRS.[508,509] Clinical manifestations include local skin reactions at the injection site, fever and influenza-like syndrome and potentially fatal acute anaphylaxis and systemic inflammatory response syndrome (SIRS). Hypersensitivity reactions may be severe enough to require aggressive management and discontinuation of therapy. Meanwhile, these antibodies have immunomodulatory effects thus they can also induce various autoimmune diseases. AEs are also common in patients receiving bsAbs, with the majority of them being grade 3 or higher-grade AEs. A phase II study which included R/R B-ALL patients revealed that the common AEs during blinatumomab therapy included pyrexia (81%), fatigue (50%), headache (47%), tremor (36%), and leukopenia (19%), and most of the AEs occurred during the first cycle of administration.[357] In another trial, patients in the blinatumomab group suffered more AEs but the rate of serious AEs in the blinatumomab group was lower than that in the chemotherapy group.[510] The T-cell activation induced by BiTE poses the risk of unique complications such as CRS, neurotoxicity and TIS.[511] Moreover, severe CRS and neurological toxicity are the main reasons for the interruption of BiTE therapy, which can be controlled by close clinical monitoring and timely preventive or therapeutic intervention.

More importantly, the immunogenicity of antibodies is not only related to the percentage of homology, as specific amino acid changes at some positions can also affect immunogenicity. Drug-induced immunogenicity has been recognized as a major challenge in the development of antibodies, resulting in adverse effects and loss of efficacy. Drug administration to patients may induce humoral immune responses, causing the formation of anti-drug antibodies (ADAs). ADAs can complex with circulating therapeutic antibodies, making it difficult to achieve efficacious levels of circulating therapeutic antibodies. ADAs may not only inactivate the drug and cause a loss of targeting and/or increased clearance of ADA-drug complexes but also induce increased toxicity caused by the immune response that accompanies ADA formation, loss of drug targeting, or formation of highly immunogenic complexes.[508,512] Therefore, ADA assays should be rationally designed to allow an understanding of the characteristics and consequences of the detected ADAs.

Both the cytotoxic molecules and the antibody portion of ADCs can affect normal cells, resulting in "off-tumor" toxicities.[513] These "off-tumor" toxicities can be divided into "on-target" and "off-target" toxicities. The "on-target" toxicity is caused by ADCs killing normal tissues that express the target antigen, while "off-target" toxicity refers to the killing of ADCs in tissues that do not express the target antigen. Based on clinical observations, "on-target toxicity" caused by small molecule toxins is the major source of adverse effects of ADCs. Both antibody-mediated ADCC and CDC effects can occur in normal cells expressing the target antigen and lead to adverse reactions such as secondary kidney injury. In addition, like mAbs and bsAbs, ADCs can block the signaling of target antigens in normal cells, resulting in adverse reactions such as lung injury and liver toxicity. The "off-target toxicity" can be caused by the shedding of cytotoxic molecules into the circulation, bystander effect on normal cells and endocytosis and uptake of ADC by normal cells, causing normal cells to suffer damage from cytotoxic molecules.[514] The main victims are lymphocytes, granulocytes, and platelets in the bloodstream, followed by kidneys, lungs, nerves, skin and other tissues, causing clinically observed side effects similar to those of chemotherapeutic drugs.[513] Common AEs include fever, nausea, infection, vomiting, and stomatitis. Severe side effects were low blood counts, liver damage including hepatic VOD, infusion-related reactions and hemorrhage. Treatment discontinuation should be considered for patients who develop obvious signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension. Premedication with a corticosteroid, antihistamine and acetaminophen is recommended about one hour prior to the administration of ADC agent.[515]

Immune-related adverse effects during ICI therapy

AEs linked to the use of ICIs are referred to as immune-related AEs (irAEs). These primarily include immune-related skin toxicity, endocrinopathies, hepatotoxicity, gastrointestinal toxicity, pulmonary toxicity, hematologic toxicity, central nervous system toxicity, cardiovascular toxicity, rheumatologic toxicity, immunotoxicity, renal toxicity, ocular toxicity, etc.). The incidence of irAEs with single-agent ICIs varies depending on the single agent, the tumor type and the disease setting.[478] Grading of irAEs is in accordance with the Common Terminology Criteria for AEs (CTCAE). Recommendations for the monitoring, diagnosis and treatment of irAEs are available in consensus guidelines from the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), the NCCN and the Society for Immunotherapy of Cancer (SITC).[516–520] In principle, there are four sequential steps in the management of irAE: (i) diagnosing and grading irAEs, (ii) ruling out differential diagnoses and workup before immunosuppression, (iii) selecting the appropriate immunosuppression strategy for grade ≥2 cases, and (iv) actively evaluating at 72 h to make treatment adjustments.[521] While the management depends on the affected organ system, in general, ICI therapy should be followed with close monitoring for grade 1 toxicities, except for some neurologic, hematologic and cardiovascular toxicities.[521] ICI therapy may be discontinued for the majority of grade 2 toxicities. Consideration should be given to resuming ICI therapy if symptoms revert ≤grade 1. Suspension of ICIs and initiation of high-dose corticosteroids is generally warranted for grade 3 toxicities. Corticosteroids should be tapered over the course of a minimum of 4 to 6 weeks. For grade 4 toxicities, permanent discontinuation of ICIs is generally recommended. This does not apply to endocrinopathies that have been controlled with hormone replacement therapy.[521,522]

Immune-related skin toxicity. Dermatologic toxicity seems to be one of the most commonly occurring AEs during treatment with ICIs.[523–527] Maculopapular eruption and pruritus are the most common symptoms. Serious dermatologic toxicities, such as

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) and acute febrile neutrophilic dermatosis (Sweet syndrome) and systemic symptoms, are rare.[524] Although serious cutaneous AEs are rare, cutaneous side events can have a significant impact on the quality of life, reduce patient compliance and lead to dose adjustments or even discontinuation of treatment.[525,528] The question of whether ICIs can be resumed after grade 3 skin toxicity has been reduced to grade 1 or less with hormonal therapy should be discussed with the dermatologist. ICIs should be discontinued permanently and patients referred to a dermatologist if severe (grade 4) herpetic dermatoses occur.[516–520]

Immune-related endocrinopathies. Immune-related endocrinopathies involving the thyroid gland (hypothyroidism or thyrotoxicosis), pituitary hypophysitis, adrenal glands (adrenal insufficiency), and pancreas (diabetes mellitus) are a frequent cause of acute and prolonged morbidity and may even be fatal.[529–533] Mild symptoms can be managed with continuation of ICI therapy with appropriate hormone replacement therapy; moderate symptoms require immediate discontinuation of ICI therapy and moderate symptoms require oral prednisolone 0.5–1 mg/kg; severe symptoms require intravenous prednisolone 1 mg/kg (methyl) tapered to 5 mg depending on symptom control, but hormone therapy cannot be discontinued. Routine monitoring of blood glucose levels is recommended in patients treated with ICIs and caution is required for the development of life-threatening ketoacidosis.[533] Unlike other irAEs, endocrinopathies are almost always permanent and require lifelong hormone replacement.[520] Due to the relatively vague nature of the symptoms associated with these endocrinopathies, prompt recognition and initiation of treatment can have a dramatic impact on a patient's health and quality of life.

Immune-related hepatotoxicity. ICI-associated hepatitis is mainly characterized by elevated levels of transaminases with mildly elevated levels of bilirubin.[534–536] The diagnosis of immune-related hepatitis may be aided by laboratory tests, which include viral serologies, liver ultrasound, cross-sectional imaging, and liver biopsy.[534] Serum transaminase and bilirubin levels are recommended for all patients receiving ICI therapy before each treatment cycle to assess liver function. Hepatitis is usually asymptomatic, with some patients presenting with low-grade fever and malaise, which may be associated with transaminase levels.[535] Most patients with immune-related hepatitis respond to corticosteroids, but a substantial fraction require treatment with a secondary immunosuppressive agent.[534] It is also important to be alert to cases in which rebound transaminase levels or even fulminant hepatitis have been observed clinically, even after transaminase levels have been reduced to normal. The patient's clinical presentation and serologic test results must continue to be monitored after recovery of liver function.

Immune-related gastrointestinal toxicity. Immune-related gastrointestinal toxicity is also a common adverse effect of ICI therapy, mainly manifested as diarrhea, colitis and small bowel inflammation.[537–540] The risk of gastrointestinal side effects is much higher with anti-CTLA-4 mAbs than with anti-PD-1/PD-L1 mAbs and can occur at any time during treatment, even months after treatment has ended. The median time for gastrointestinal side effects was 3 months. Following the diagnosis of immune-related gastrointestinal adverse events, the clinical selection of treatment options was based on the severity and duration of diarrhea. In addition to discontinuation of ICI, patients with grade 1 diarrhea may be treated with antidiarrheal drugs alone (loperamide, etc.) based on active rehydration and correction of water-electrolyte imbalance; for grade 2 diarrhea and above, glucocorticoids are the first recommended treatment; for grade 3–4 diarrhea or if glucocorticoid therapy is ineffective, immunosuppressive agents (e.g, infliximab, vedolizumab) are also an option.

Immune-related pulmonary toxicity. Immune-related pulmonary toxicity is a heterogeneous group of disorders that includes various clinical manifestations such as interstitial lung disease (ILD) or pneumonitis and rarer presentations such as bronchiolitis or pulmonary sarcoidosis.[519,541–543] Immune-related pulmonary toxicity usually appears in the first few months and is accompanied by non-specific clinical manifestations but with suggestive radiologic signs.[544] Exploratory endoscopy, including bronchoalveolar lavage and transbronchial lung biopsies, can further refine the diagnosis by ruling out a lung infection and demonstrating lymphocytic alveolitis. Any new respiratory symptoms, such as upper respiratory tract infection, cough, wheezing and dyspnea, should prompt a chest CT (computerized tomography) scan. Follow-up and monitoring are recommended for those who have imaging changes only and no clinical symptoms (grade 1); prednisolone therapy is suggested for those with mild to moderate symptoms (grade 2) and those with severe or life-threatening symptoms. For grade 2 pneumonia, clinical symptoms should be evaluated every 2–3 days; for grade 3–4 pneumonia, clinical symptoms and imaging should be evaluated after 2 days of treatment and if there is no evidence of improvement, immunosuppressive agents such as infliximab, cyclophosphamide, or mycophenolate mofetil can be considered.[517–519]

Other rare immune-related toxicities. Rare immune-related toxicities during ICI treatment mainly include neurotoxicity, cardiotoxicity, rheumatologic immunotoxicity, hematologic toxicity, neuromuscular toxicity, and nephrotoxicity.[545–553] However, they are still reported in 1–12% of cases and are more common in patients receiving combination therapy. As an increasing number of patients with cancer are being treated with checkpoint inhibitors, the balance between clinical benefits and treatment-related toxicities for each patient is becoming more challenging.[554] Rarity is not the same as insignificance and the extent of damage to patients after its occurrence can even lead to death in a short period of time. In general, patients who experience a severe grade 3 or 4 irAE during ICI therapy are at risk of experiencing serious toxicities when rechallenged with checkpoint inhibitors.[555]

CAR-T therapy-related toxicities

Cytokine Release Syndrome (CRS) and neurotoxicity are the most common and unique toxicities associated with CAR T-cell therapies,[556–567] and they are completely different from the irAEs that are associated with the treatment of ICIs. CAR-based therapies have the advantage of higher targeting specificity over conventional chemotherapy and radiotherapy. However, like antibody-based therapies, targeted antigens od CAR-T cells are also expressed in normal cells, such as CD19 in the normal B-cell lineage. The "on-target, off-tumor" toxicity is widespread, although a large part of others has not been identified or overlapped with other symptoms. Some toxicities, such as hypogammaglobulinemia, are a direct consequence of the "on-target, off-tumor" effects of the CAR-T cells and others may be an indirect result of the immunosuppressed state of the host.[565] For early recognition of potential toxicities and timely intervention, clinical monitoring before, during and after CAR-T cell therapy is critically required. Perhaps more importantly, with the appropriate management strategies, some of these toxicities associated with CAR-T therapies can be reversed with appropriate monitoring and management (Table 4).[559,568–570]

CRS. CRS is the most common life-threatening adverse event associated with CAR T-cell therapy. Variable incidence of CRS has been reported with different CAR T-cell therapies due to

differences in grading scales used to assess CRS severity, CAR T-cell design and generation and clinical trial design.[565,571] The typical time to the onset of CRS ranges from 2 to 3 days, with a persistent duration of 7 to 8 days, although CRS can occur within a few hours or as late as 10 to 15 days after CAR-T cell infusion. The onset of CRS is usually characterized by fever and constitutional symptoms such as malaise and anorexia. In severe cases, CRS also manifests with features of a systemic inflammatory response. These include hypotension, hypoxia, cytopenia, coagulopathy and even organ dysfunction. The organ dysfunction may be the secondary effect of hypotension or hypoxia, but it may also be a direct result of the release of cytokines. Organ dysfunction can be prevented or even reversed in the majority of patients if the symptoms and signs of CRS are recognized and addressed in a prompt and timely manner.[564] CAR-T cell-mediated cancer elimination was also the trigger for the systemic inflammatory response, which is the hallmark of CRS.[556,558,572] Thus, from a clinical standpoint, the most important management to overcome CRS is to block the feedback loop of cytokines.[573] Cytokines and markers of inflammation that have been implicated in more severe CRS are C-reactive protein (CRP), ferritin, interferon (IFN)-γ, IL-1, IL-2, soluble IL2-Rα, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, granzyme B, granulocyte/macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1α (MIP-1α), and monocyte chemoattractant protein-1 (MCP-1).[564,574–577] A number of risk factors for severe CRS have been implicated, although these vary between different studies and likely between different indications. In general, these include an increased CAR-T cell expansion and a higher tumor burden.[578,579] Moreover, bone marrow (BM) suppression is also considered a determinant of the occurrence and evolution of CRS.[579] Because the management of CRS depends on the severity of the disease, several institutions had independently developed different CRS grading systems prior to the publication of consensus guidelines. These guidelines have contributed to the standardization of CRS management. Both direct targeting and non-specific immunosuppressive strategies to counteract overactive immune cells and elevated cytokine are used to control CRS in patients receiving CAR T-cell therapy. IL-6 has been implicated as an activating signal for CAR-T cells and is considered a pivotal mediator of CRS. The empirical testing of various blocking antibodies soon identified IL-6 as a critical driver of CRS. Tocilizumab, a monoclonal antibody that blocks signaling through the IL-6 receptor (IL-6R), became a cornerstone of CRS management.[564,580–583] In general, patients with grade 1 CRS should be given broad-spectrum antibiotics along with supportive care. This may vary depending on the end-organ toxicities that are observed. Intravenous tocilizumab should be administered for a maximum of 4 doses to patients with grade ≥2 CRS. In cases of grade ≥3 CRS and in cases of grade 2 toxicity with sustained hypotension after anti-IL-6 therapy, the addition of corticosteroids should be considered.[518] To prevent the progression of CRS, emergent intervention is warranted. However, other potential causes of the inflammatory response, including infection and malignant progression, should be ruled out. If there is no

Table 4. Monitoring and management of toxicities associated with CAR-T therapy

CAR-T therapy-related AEs	Biomarkers to monitor	Toxicity management
CRS	CRP, IFN-γ, IL-1, IL-2, IL2Rα, IL-4, IL-6, IL-8, IL-10, TNF-α, granzyme B, MIP-1α, MCP-1, and GM-CSF in PB	Grade 1: broad-spectrum antibiotics along with supportive care; Grade ≥2: Intravenous tocilizumab ≤4 doses; Grade ≥3 and in cases of grade 2 toxicity with sustained hypotension after anti-IL-6 therapy: add corticosteroids; Refractory to both tocilizumab and corticosteroids: use other agents include the Janus-associated kinase inhibitor, cyclophosphamide, extracorporeal cytokine adsorption with continuous renal replacement therapy, IVIG and anti-thymocyte globulin.
Neurotoxicity	IL-1, IL-6, IFN-γ, TNF-α/β, CRP, coagulation markers, ferritin in PB; MCP1, IL-6, IL-8 in CSF; ICE score	Grade ≥1 ICANS: monitoring, supportive care and corticosteroids alone; Tocilizumab was not recommended unless patients have concurrent CRS.
HLH/MAS	Blood routine test; IFN-γ, IL-6, GM-CSF, CRP, ferritin in PB	Suppress the overactive immune cells; Corticosteroids, anakinra or intrathecal cytarabine can be considered in cases when the HLH/MAS is caused by resistance to tocilizumab.
CARAC	Primary coagulation markers including platelet count in PB, APTT, PT, FIB, FDP, and D-dimer; test for CRS	Management of CRS; replacement therapy to decrease the risk of bleeding and control active bleeding, including the transfusion of platelet, fresh frozen plasma and prothrombin complex concentrates and fibrinogen and cryoprecipitate; anticoagulant therapy and/or antifibrinolytic therapy should be used as appropriate for patients with high-grade CRS.
Cytopenia	Blood routine test, CRP, ferritin in PB; cytology of blood marrow	Growth factors, thrombopoietin receptor agonists, stem cell enhancement, transfusion support; Elimination of infectious risk
Hypogammaglobulinemia	Gammaglobulinemia in PB	Intravenous or subcutaneous immunoglobulin G
Infection	IL-6, CRP in PB; lymphocyte count; CT of lungs; viral and bacterial etiologic test	Provide antibacterial or antifungal prophylaxis; For certain patients with concurrent severe or recurrent infections and hypogammaglobulinemia: IVIG is recommended as replacement treatment.
ADAs	Detection of ADAs in serum (HAMA is the ADA occurred in CAR-T therapy with murine-derived scFv)	Secondary reinfusion by altering the target and strengthening lymphodepletion.

CAR-T chimeric antigen receptor T cell, *AEs* adverse effects, *CRS* cytokine release syndrome, *CRP* C-reactive protein, *IFN* interferon, *IL* interleukin, *TNF* tumor necrosis factor, *MIP* macrophage inflammatory protein, *MCP* monocyte chemoattractant protein, *GM-CSF* granulocyte/macrophage colony-stimulating factor, *PB* peripheral blood, *IVIG* intravenous immunoglobulin G, *CSF* cerebrospinal fluid, *ICE* immune effector cell associated encephalopathy, *ICANS* immune effector cell-associated neurotoxicity syndrome, *HLH/MAS* Hemophagocytic lymphohistiocytosis/macrophage activation syndrome, *CARAC* CAR-T therapy-associated coagulopathy, *APTT* activated partial thromboplastin time, *PT* prothrombin time, *FIB* fibrinogen, *FDP* fibrin degradation products, *CT* Computed Tomography, *ADA* anti-drug antibody, *HAMA* human-anti-mouse antibody, *scFv* single chain variable fragment

improvement in CRS after treatment with tocilizumab and steroids, an examination for infection should be performed and managed as necessary. In addition to siltuximab and anakinra, other agents may be considered for patients who are refractory to both tocilizumab and corticosteroids. These agents include the Janus-associated kinase inhibitor, cyclophosphamide, extracorporeal cytokine adsorption with continuous renal replacement therapy, intravenous IgG (IVIG) and anti-thymocyte globulin. Data in support of the use of any of these agents are mostly from anecdotal reports or small case series.

Neurotoxicity. Neurotoxicity is another adverse event that has been a concern in clinical trials of various immune effector cell therapies.[577,584,585] Neurologic toxicity may occur concurrently with CRS. However, in some cases, neurologic toxicity may not occur simultaneously but may occur before or days after CRS. Like CRS rates, neurotoxicity incidence rates across clinical trials vary considerably. Neurologic toxicities are diverse and may include temporary working memory loss, delirium, seizures and rarely, acute cerebral edema.[564] Neurotoxicity associated with CAR T-cell therapies has been referred to as immune effector cell-associated neurotoxicity syndrome (ICANS). It is characterized by a pathologic process involving the central nervous system following any immunotherapy that results in the activation or engagement of endogenous or infused T cells and other immune effector cells. The time to the onset of neurotoxicity is typically 4–10 days after the administration of CAR-T cells, with a duration of 14–17 days. For BCMA-directed CAR T-cell therapies, the duration may be somewhat shorter. CRS is considered to be a potent risk factor for ICANS and the severity of CRS is highly correlated with that of ICANS. The development of neurotoxicity is associated with a higher pretreatment disease burden, a higher peak CAR T-cell expansion, a higher baseline inflammatory status, an earlier and higher elevation of pro-inflammatory cytokines in the blood and cerebrospinal fluid and the presence of pre-existing neurological comorbidities.[563] Pro-inflammatory cytokines were accumulated in the cerebrospinal fluid during severe neurotoxicity, with a disproportionately high level of IL-6, IL-8, and MCP1, suggesting a production that is specific to the central nervous system.[563] IL-1, derived from monocytes, has recently been highlighted as a key driver of neurotoxicity.[556] Gust et al. also described the endothelial dysfunction and increased permeability of the blood-brain barrier (BBB) during neurotoxicity following adoptive immunotherapy with CD19 CAR-T cells, which may help to identify risk predictors for neurotoxicity.[585] Increased BBB permeability may enable inflammatory cytokines and immune cells to migrate into the central nervous system and potentially contribute to inflammation of the nervous system.[585,586] As in the case of CRS, the risk factors and the incidence of CRS are reported with variability between studies. CD19-directed CAR is more likely than BCMA-directed CAR to be accompanied by high-grade ICANS. The grade of ICANS determines the management of neurotoxicity. Consensus guidelines with recommended grading of ICANS have been issued by the American Society for Transplantation and Cellular Therapy (ASTCT). It's recommended that clinicians use this scale to grade any CAR-T cell-related neurotoxicity.[587,588] Along with careful monitoring and supportive care, corticosteroids are the cornerstone of ICANS management. Since tocilizumab may exacerbate ICANS,[575] for patients with grade 1 CRS (fever only) and higher grade ICANS, corticosteroids alone may be preferred. The NCCN consensus panel does not recommend treating patients receiving CAR T-cell therapy for neurotoxicity with tocilizumab unless they have concurrent CRS.[518]

Hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) is regarded as a serious immunologic syndrome that is triggered by out-of-control immune activation, which includes the hyperactivation of macrophages and lymphocytes, increased production of pro-inflammatory cytokines, infiltration of lymphocytes and histiocytes into tissues and organs and multi-organ failure.[569,584,589,590] In contrast to primary HLH/MAS, CAR T-cell therapy-induced HLH/MAS is thought to be a type of secondary HLH/MAS because it is initiated by an immune trigger.[558] In a recent study, it was estimated that HLH/MAS occurs in 3.5% of the patients who receive CAR T-cell therapy.[591] Nevertheless, the actual incidence of HLH/MAS has been disputed, in part because of the close overlap in symptoms between CRS and HLH/MAS. The definitive diagnosis of HLH/MAS after CAR T-cell therapy can be challenging as the clinical features and laboratory abnormalities overlap substantially with the CRS.[558,591] The majority of patients with moderate-to-severe CRS exhibit the typical laboratory abnormalities of HLH/MAS, such as elevated levels of CRP, cytopenia, hyperferritinemia, hypofibrinogenemia, coagulopathy, and increased levels of several serum cytokines, in particular IL-6, INF-γ and GM-CSF.[478,569,584,589] The clinical manifestations related to CAR T cell-induced HLH/MAS typically comprise fever, multi-organ dysfunction and central nervous system disorders and occasionally hepatosplenomegaly or hemophagocytosis in the bone marrow or other organs.[589,591] Suppressing the overactive immune cells that are contributing to symptoms is the ultimate goal of clinical management of HLH/MAS. In some cases, resistance to tocilizumab may also lead to late-onset HLH/MAS-like lesions. Corticosteroids, anakinra, or intrathecal cytarabine should be considered in such cases.[584,589,590] However, there is still a lack of data to support the use of such drugs in this setting.

Hypogammaglobulinemia. Hypogammaglobulinemia is another potential risk related to CAR T-cell therapy. Hypogammaglobulinemia has been reported in up to 53% of patients who have been treated with CAR-T cells in clinical studies.[592,593] Hypogammaglobulinemia is a disorder that is characterized by decreased levels of antibodies in the blood and an increase in the risk of infection. Hypogammaglobulinemia is the consequence of an extremely small number of B cells or plasma cells, termed B cell aplasia or plasma cell aplasia, respectively.[593] Even in patients in CR after CAR T-cell therapy, long-term hypogammaglobulinemia may still occur. The recommendations are made based on experts' opinions, institution-specific experience and infection prevention approaches and strategies from other contexts due to the lack of randomized, controlled clinical trials for the treatment of hypogammaglobulinemia.[593] Hypogammaglobulinemia can be controlled with either intravenous or subcutaneous immunoglobulin G, a product of fractionated blood derived from the pooled plasma of many individuals.[592–595] Immunoglobulin offers broad protection from opportunistic infections because it contains antibodies against a variety of infectious agents.[592]

Cytopenia. Patients receiving CAR T-cell therapy are also at high risk for developing hematologic toxicities, particularly sustained cytopenia such as neutropenia, thrombocytopenia, anemia and/or leukopenia.[596–598] Cytopenia may appear following CAR-T infusion and always presents at an early stage (<30 days), frequently for a prolonged period (30–90 days) and sometimes persists or appears at a late stage (>90 days).[597] The onset and duration of cytopenia are often correlated with the severity of CRS and ICANS, the burden of the tumor, the number of prior therapies, baseline blood counts, peak levels of CRP and ferritin, as well as the CAR construct.[596,597,599,600] Bone marrow biopsy is critical for the evaluation of both primary disease and secondary bone marrow neoplasm in patients with persistent or late-onset cytopenia. The management options for cytopenia are somewhat limited and need to be individualized based on the likely underlying etiology. These options may include growth factors, thrombopoietin receptor agonists, stem cell enhancement, transfusion support and the elimination of infectious risk.[597,601,602]

Coagulopathy. The typical time to onset of CAR-T therapy-associated coagulopathy (CARAC) is often 6 to 10 days after CAR-T cell infusion and closely follows the elevation of IL-6 and other cytokines and gradually relieves as the CRS is controlled.[503] CARAC, including disseminated intravascular coagulation (DIC), prolonged prothrombin time/activated partial thromboplastin time, and hypofibrinogenemia, often occurs in patients with severe CRS.[603] Over half of the patients experienced thrombocytopenia or at least one abnormal coagulation parameter after CAR-T therapy. Clinically bleeding events occurred in about 19.6% of patients with coagulopathy and 14 to 50% of patients with coagulopathy developed DIC; 6.7 to 42.9% of patients with DIC died.[503] Monitoring of patients with CARAC is imperative to avoid the potential for bleeding events and even life-threatening hemorrhage. Since the severity of CARAC is highly associated with that of CRS, the management of CRS is of great importance. As bleeding is the main feature of CARAC, replacement therapy can decrease the risk of bleeding and control active bleeding, including the transfusion of platelet, fresh frozen plasma and prothrombin complex concentrates and fibrinogen, and cryoprecipitate. More importantly, anticoagulant therapy and/or antifibrinolytic therapy should be used as appropriate for patients with high-grade CRS.[503]

Infection. Infectious complications following CAR T-cell therapy are very common. They have been reported in up to ~70% of recipients.[604–606] The majority of infections develop shortly following infusion and can be attributed to several causes, such as the depletion of normal B cells or plasma cells resulting from the direct action of the CAR-T cells, the depletion of lymphocytes and granulocytes caused by conditioning chemotherapy, anti-cytokine, or corticosteroid therapies given for CRS or neurologic toxicity and immunocompromise induced by the patient's underlying malignancy.[604,607] Infections, including bacterial, viral and fungal infections, have been reported following CAR T-cell therapy and can be life-threatening.[604] An increased likelihood of acute infections may also be linked to the seriousness of CRS. The control of infections is generally with agents that are selective for the source of the infection. Risk stratification should be performed based on patient characteristics such as prior suppressive therapy, history of infection, etc. when determining whether to provide antibacterial or antifungal prophylaxis.[604] For certain patients with concurrent severe or recurrent infections and hypogammaglobulinemia, the NCCN guidelines suggest IVIG as a replacement treatment.[518]

ADA. Since CAR is an exogenous sequence, it has certain immunogenicity which leads to ADA production by humoral immunity after infusion. Early-generation CAR-T cells were constructed from murine-derived scFv and the species difference resulted in the generation of a HAMA.[276] Even though humanized CAR circumvented immunogenicity to a certain extent, some patients were still reported to have ADA in clinical trials of CD19 and BCMA, which eventually affected the efficacy or led to earlier relapse.[278,608] Therefore, monitoring of ADA has become an important part of current CAR-T clinical trials. Although with large individual variability, the factors related to the production of ADA are currently thought to be the use of CAR-T with murine scFv and multiple infusions of the same CAR-T product.[275,609] There is no targeted method to solve the problem of ADA, but it should be monitored by ELISA (enzyme-linked immunosorbent assay) and flow cytometry, to understand the reason for drug resistance or recurrence in patients in time,[610,611] and to reduce the impact of ADA on secondary reinfusion by replacing the target and strengthening lymphodepletion.[609,612]

CHALLENGES AND FUTURE PROSPECTS

Each immunotherapy strategy has achieved varying degrees of encouraging results in hematologic malignancies. Different immunotherapeutic approaches have their advantages but also shortcomings that need to be addressed (Table 5). Further clinical exploration will be needed to further improve the prognosis of patients with hematologic malignancies. The allo-HSCT remains the primary treatment for hematologic malignancies with a potentially curative outcome. The haplo-HSCT modality can best address the limited source of allo-HSCT donors, but it's still necessary to further explore how to minimize the severity of GVHD and transplant-related death while improving anti-tumor effects, especially for patients with R/R hematologic cancers. The future direction of transplantation will be toward personalization, in which a combination therapy strategy is very essential. R/R patients can be pre-treated with CAR-T therapy or other targeted therapies to achieve remission before bridging to HSCT. Patients, who still have residual disease after incomplete remission with various treatments such as chemotherapy, targeted therapy and immunotherapy, can be treated with donor CAR-T combined with allo-HSCT. For patients with positive MRD after transplantation, CAR-T therapy can also be recommended. The second direction is to optimize donor selection, especially for familial donors and to avoid selecting donors who carry the same genetic defect as the patient. Molecular testing can be used to detect HLA loss and guide the search for donors for patients who need a second transplantation. In addition, anti-tumor therapy needs to be considered along with GVHD prevention and thus individualized management should be conducted after transplantation to balance the anti-GVHD and anti-tumor benefits. The mAbs, bsAbs, and ADC-based agents have also improved the treatment of cancer patients to some extent, but the clinical toxicities remain unavoidable. Meanwhile, some patients have demonstrated little or no responsiveness to such treatments. Ideal tumor antigens need to be screened for these antibody-based therapies to improve the anti-tumor effects and reduce the incidence of "off-tumor, on-target" effects. The technical threshold for the development of bsAbs is more difficult compared to single-target mAbs. Selecting the best target combination is only the first step, followed by a rational structural design based on the receptor structure as well as the biological mechanism of the disease. In addition, inappropriate clinical design and dosing regimens will result in higher toxicity in patients, which can be improved by optimizing treatment strategy, dose and timing to reduce side effects to some extent. The payload and linker in ADC drugs can also directly affect effectiveness and safety. In addition, how to solve the complexity of pharmacokinetics, enhance drug stability, improve drug efficacy and reduce drug resistance are also urgent to be explored. The bsADC (bispecific antibody-drug conjugate) combines the advantages of bsAbs and ADCs and is a major challenge for the future. Compared to mAbs, bsADCs can target tumor cells more specifically through two antibodies, overcoming drug resistance while increasing the safety. Meanwhile, novel therapeutic agents, such as bifunctional checkpoint-inhibitory T cell engager (CiTE),[613] simultaneous multiple interaction T cell engager (SMITE),[614] trispecific killer engager (TriKE) and BiTE-expressing CAR-T cells, are being designed to integrate various immune functions into one molecule or a single cellular vector and thereby enhance efficacy without compromising safety.[172] ICIs have shown superior efficacy mainly in HL and primary mediastinal large B-cell lymphoma, but has limited efficacy in other hematologic cancers. Serious irAEs may also occur with ICI therapy, which will impede its application in the clinic. The exploration of more-effective and rational combinatorial approaches is an area of great interest in improving the efficacy of ICI therapy. The emergence of ACTs, especially CAR T-cell therapy, offers a new therapeutic avenue and hope for R/R patients with hematologic malignancies. However, these therapeutic approaches are usually accompanied by serious complications such as CRS, ICANS, and "off-target" effects, while achieving remarkable results. Challenges remain in the optimization of CAR

Table 5. The advantages and limitations of various immunotherapies in hematologic malignancies

Type of immunotherapy	Advantages	Limitations	Future directions
allo-HSCT	The only option to achieve a cure for hematologic malignancies.	Incidence of transplant related mortality and graft-versus-host disease.	Personalization and combination therapy; optimization of donor selection, maintenance therapy to balance the anti-GVHD and anti-tumor benefits.
mAb	Specifically targeting tumor antigen and inducing cancer cell death; their combination with chemotherapy has been first-line therapy for several cancers.	Incidence of "off tumor, on target" effect and therapy-related toxicities.	Requirement for suitable target antigen; optimization of treatment strategy; overcome drug resistance to single-agent therapies.
bsAb	Combining the binding sites of two monoclonal antibodies in the same one molecule to promote cancer cell killing.	Incidence of "off tumor, on target" effect and therapy-related toxicities; a lack of co-stimulation might induce T-cell anergy and compromise the clinical efficacy;	Requirement for suitable target antigen; need to selecting the best target combination; require rational structural design; optimization of treatment strategy; overcome drug resistance to single-agent therapies.
ADC	Utilizing the specific binding properties of mAb to selectively deliver cytotoxic agents to cancer cells to increase the therapeutic potentials of cytotoxic agents.	Incidence of "off tumor, on target" effect and therapy-related toxicities.	Requirement for suitable target antigen; require rational structural design; solve the complexity of pharmacokinetics, enhance drug stability, improve drug efficacy and reduce drug resistance; optimization of treatment strategy; design of bsADCs; overcome drug resistance to single-agent therapies.
ICI	Blockade of immunosuppressive checkpoint signaling pathway.	Incidence of irAEs; only the therapeutic results in HL was remarkable.	Overcome drug resistance to single-agent therapies; combination therapy with epi-drugs, CAR-T therapy and/or HSCT.
CIK, γδ T and NK cells	Non-specific cellular therapies; no demand for genetical modification.	Requirement for a large number of cells; limited efficacy in hematologic malignancies.	Improvement of clinical efficacy and reduction of toxicity; combination therapy with epi-drugs, ICIs and/or HSCT.
CAR-T cell therapy	Specific cellular therapies; no restriction of MHC; achieve rapid development and great success in treating hematologic malignancies, especially R/R patients; serve as the "bridge" to transplant; several cell products have achieved FDA's approval and entered into the commercialized field.	Therapy-related toxicities, such as CRS and neurotoxicity; long period of manufacturing; high cost.	Requirement for suitable target antigen; optimization of CAR design and cell products; improvement of remission rates; prolongation of remission duration; reduction of toxicity and expansion of this therapeutic modality to other cancer types; universal CAR-T products; overcome drug resistance to monotherapy; combination therapy with epi-drugs, ICIs and/or HSCT.
CAR-NK cell therapy	Specific cellular therapies; no restriction of MHC; provide an "off-the-shelf" cell product and could be readily available for immediate clinical use; serve as the "bridge" to transplant.	Still in early stage of clinical studies; limited efficacy in hematologic malignancies.	Requirement for suitable target antigen; optimization of CAR design and cell products; improvement of clinical efficacy and reduction of toxicity; expansion of this therapeutic modality to other cancer types; overcome drug resistance to monotherapy; combination therapy with epi-drugs, ICIs and/or HSCT.
Tumor vaccine	Taking advantage of tumor-associated antigens or tumor-specific antigens to stimulate the immune system.	Still in very early stage of clinical study; limited efficacy in hematologic malignancies.	Requirement for suitable target antigen and vaccine vectors; improvement of clinical efficacy and reduction of toxicity.

allo-HSCT allogeneic hematopoietic stem cell transplantation, *mAb* monoclonal antibody, *bsAb* bispecific antibody, *ADC* antibody-drug conjugate, *bsADC* bispecific antibody-drug conjugate, *ICI* immune checkpoint inhibitor, *HL* Hodgkin lymphoma, *irAEs* immune-related adverse effects, *MHC* major histocompatibility complex, *R/R* refractory and relapsed, *FDA* Food and Drug Administration, *CIK* cytokine-induced killer cells, *γδ* T gamma/delta T, *NK* natural killer, *CAR-T* chimeric antigen receptor T, *CRS* cytokine release syndrome

design and cell products, improvement of remission rates, prolongation of remission duration, reduction of toxicity and expansion of this therapeutic modality to other cancer types. To further improve patient outcomes, innovative strategies are needed to enhance the therapeutic efficacy and in vivo persistence of CAR-T cells and to mitigate tumor cell resistance. Elucidation of mechanisms of resistance and immune escape has long been a big challenge. Epigenetic mechanisms play an important role in both tumor development and anti-tumor immune regulation and epi-drugs represented by DNA methylation inhibitors and histone deacetylation inhibitors can coordinate, potentiate and reduce immune escape effects in several aspects by regulating tumor killing and enhancing the anti-tumor immunity.[615–617] Therefore, a deeper and broader exploration of epi-immunotherapy will further advance the understanding of this emerging concept and bring more creative breakthroughs in immunotherapy. Allogeneic CAR-T cells also have the potential to overcome many of the manufacturing limitations of traditional autologous CAR T-cell therapies.

Universal CAR-T cells will undoubtedly be the future direction of CAR-T therapy. While there are still concerns about host-versus-graft and graft-versus-host reactions caused by CAR-T cells in the allogeneic environment, the risks and side effects are being reduced through gene knockout technology and the safety of universal CAR-T cells will be further enhanced. Universal CAR-T therapies are expected to bring less expensive and more immediately available "off-the-shelf" therapies to patients with malignant hematologic cancers. However, there are many challenges with universal CAR-T cells and clinical studies are still in the early stages. Tumor vaccines take advantage of tumor-associated antigens or tumor-specific antigens to stimulate the immune system but are currently in their infant stage and there is still much space for refinement to discover their full potential.

The current status quo in cancer treatment is that immunotherapy is generally used as a second-, third-, or even last-line treatment option when patients have no better options. Based on promising results in terms of efficacy and safety, immunotherapy is expected to become the first line of treatment in the future, while conventional treatment will be relegated to the second line.[618] Treatment regimens for patients with hematologic cancers typically include 3–4 or even 5 cytotoxic drugs and the addition of immunotherapy drugs can reduce the use of these chemotherapy agents. Several clinical trials have confirmed that the combination of immunotherapy with reduced chemotherapy regimens has improved rather than suppressed therapeutic effects. Therefore, one of the major trends in cancer treatment is that immunotherapy will become increasingly prominent.[618] Combination immunotherapy is an exciting area of research that may further enhance our ability to utilize the immune system against hematologic malignancies. Currently, HSCT remains a fundamental treatment option and combining HSCT with novel immunotherapies is a promising direction for our future. Many clinical questions remain to be answered. Which immunotherapy works best in the context of HSCT? Which immunotherapy is better suited as a bridge to HSCT or as a preferred option after HSCT relapse? Which immunotherapy approach is more appropriate for patients who are ineligible for HSCT? With the continuous development and advancement of molecular biology and immunology technologies, immunotherapy is expected to further change the existing treatment paradigm of hematological cancers. The detailed information generated by multidimensional omics technologies, single-cell sequencing and others will not only provide insights into the complex determinants of efficacy and toxicity of immunotherapies but also help identify predictive biomarkers and develop new treatment strategies. As future research helps to address these challenges, these advanced technologies may eventually become the standard and necessary tool in the field of immunotherapy, revealing the relationship between key drivers of cancer phenotypes and enabling clinicians to better predict and monitor patient responses, thereby facilitating more comprehensive and realistic personalized treatments for cancer patients.[619–632]

CONCLUSION

Malignant hematologic cancers are major diseases that pose a serious threat to human health. The past and present are very exciting eras for immunotherapy of hematologic malignancies, but the future looks quite incredible and we are rapidly moving in that direction. Although the various immunotherapies aim to treat cancer patients through different mechanisms of action, the core is to restart and maintain the "Cancer-Immunity Cycle" and restore normal anti-tumor immunity. Multiple categories of immunotherapies have been developed for the treatment of blood cancers and are being further evaluated in clinical trials. More importantly, some of these immunotherapies have been approved by the FDA for the treatment of blood cancers or have even entered the commercialization stage. At present, immunotherapy for blood cancers still faces a series of challenges. The most important of these is safety, where different therapies are accompanied by varying degrees of treatment-related side effects, thus emphasizing the importance of early detection and intervention of toxicities. As mentioned above, clinical experts have been developing guidelines for the management of toxicities based on clinical trials and real-world clinical experience. The establishment of these guidelines has provided a solid foundation for improving the safety and widespread use of immunotherapy. In addition, they are gaining experience in managing the unique complications associated with novel immunotherapies and establishing practice guidelines that will be critical to expanding their use worldwide. Another notable issue is treatment failure due to resistance and relapse. This illustrates the striking difference in the ability of each patient to respond to immunotherapy, highlighting the potentially urgent need for and importance of personalized cancer treatment.

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AUTHOR CONTRIBUTIONS

L.T. and H.M.: conception and offering critical comments. L.T., Z.H., and H.M.: data collection. L.T., Z.H., and H.M.: writing and original draft preparation. L.T. and Z.H.: table and figure preparation and editing. L.T., Y.H., and H.M.: review and editing. All authors contributed to the article have read and approved the submitted version.

ADDITIONAL INFORMATION

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