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γδ T cells in hematological malignancies: mechanisms and therapeutic strategies

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Abstract

γδ T cells are a unique subset of lymphocytes with both innate and adaptive features. They recognize and eradicate various hematological malignancies through different mechanisms, employing factors including γδ TCR, NKR, NKG2D, TRAIL, and perforin/granzyme. They also modulate other immune cells to enhance their antitumor activity. Moreover, γδ T cells have potent antiviral functions after hematopoietic stem cell transplantation (HSCT), which may improve the outcome of patients with hematological malignancies. In this review, we summarize the current knowledge on γδ T cell biology and function in hematological malignancies and HSCT complications. We also discuss the challenges and limitations of the clinical application of γδ T cells, such as their low frequency in peripheral blood and heterogeneity among different subsets. We then highlight some promising strategies for γδ T cell-based therapy, such as using agonist antibodies, cell engagers, or genetic modification technology. Furthermore, we review the recent clinical trials evaluating the safety and efficacy of γδ T-cell therapy in different hematological malignancies. In conclusion, γδ T cells represent a promising immunotherapeutic tool for hematological malignancies that deserves further exploration.

Key Words: γδ T; Hematological malignancies; Immune cell therapy

1. INTRODUCTION

Hematological malignancies are a heterogeneous group of cancers that originate from blood cells or their precursors. They include leukemia, malignant lymphoma, myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS), and multiple myeloma (MM). These diseases are characterized by high incidence and mortality rates, especially among children and adolescents. The current standard treatment for hematological malignancies is chemotherapy combined with hematopoietic stem cell transplantation (HSCT), which can achieve long-term remission or cure for some patients. In spite of this, leukemia and non-Hodgkin lymphoma still rank in the top 10 in estimated new cases and deaths.[1] HSCT is the transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, umbilical cord blood, or peripheral blood in order to reset the patient's hematopoietic and immune system. However, patients who receive allogeneic HSCT are always accompanied by inevitable complications like graft-versus-host disease (GvHD), infection, or relapse, which are the main causes of death after HSCT.[2] Therefore, there is an urgent need for novel therapeutic strategies that can improve the survival and quality of life of patients with hematological malignancies.

γδ T cells are a subset of T lymphocytes that express the γδ T-cell receptor (TCR) instead of the αβ TCR. Unlike conventional αβ T cells that recognize peptide antigens presented by major histocompatibility complex (MHC) molecules, γδ T cells recognize nonpeptide antigens such as phosphoantigens (PAgs) or stress-induced molecules in an MHC-unrestricted manner.[3,4] Therefore, γδ T cells can respond rapidly to exogenous pathogens and endogenous tumor cells without prior sensitization. In conclusion, γδ T cells play extensive roles in immune surveillance and anti-infection activity. In fact, there exist several subsets of γδ T cells, which distribute in different tissues and obtain various capabilities. Although γδ T cells are generally considered to possess robust anticancer ability, the interleukin (IL)-17A-producing γδ T cells are demonstrated that play an active role in inflammation,[5] autoimmune dieases,[6] and protumor activities.[7] Besides, γδ T cells reside in specific tissues and are essential for body homeostasis.[8,9] Overall, γδ T cells play a pivotal role in bridging innate and adaptive immunity and clarifying their specific responsibilities under different circumstances is needed.

In recent years, immunotherapy has emerged as a new pillar for hematological malignancy treatment, showing remarkable efficacy and safety in clinical trials.[10,11] Among the different types of immune cells that can be used for adoptive cell therapy, γδ T cells have attracted considerable attention due to their unique features and functions. Accumulating evidence indicates that γδ T cells display a robust tumor cell-killing capacity. Unlike

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conventional αβ T cells, γδ T cells recognize tumor antigens in an MHC-unrestricted manner and cause minimal GvHD, making them an attractive "off-the-shelf" product. In this review, we provide an overview of different subsets of γδ T cells, discuss their mechanisms and application in hematological malignancies treatment and HSCT settings, and focus on novel strategies of γδ T-cell therapy, with the purpose of providing a brief review of γδ T cells in hematological malignancies.

2. IDENTITIES OF γδ T Cells

2.1. Subsets and origins of γδ T cells

γδ T cells are a diverse set of cells carrying distinct γδ TCR chains. They exhibit great heterogeneity with distinct tissue localization and function. Human γδ T cells are usually classified into Vδ1, Vδ2, and Vδ3 subsets according to their TCRδ chain. In the light of TCRγ chain usage, Vδ2 T cells are the main subset of γδ T cells and usually interact with Vγ9. They predominate in peripheral blood and account for 1% to 10% of lymphocytes in human peripheral blood.[12] Unlike Vδ2 T cells, Vδ1 T cells and Vδ3 T cells are rare and mainly reside in mucosal tissues.[13]

γδ T cells were first defined by their expression of γδ TCR genes in the mid-1980s.[14–16] Studies of γδ T cells development are usually in mice, only a few studies have examined γδ T cells in human. In mice, the intrathymic development of γδ T cells appears in fetal.[17] They originate from common thymic precursors as αβ T cells and branch from double-negative (DN) thymocytes stage. Differently, γδ T cells develop and depart from the thymus in coordinated and successive waves, which are in the following order: the dendritic epidermal T cells, the IL-17-producing γδ T (γδ T17) cells, and the γδ NKT cells.[18] Similarly to mice, the first γδ T cells developed in human thymus are Vγ9Vδ2 T cells and then the Vδ1 T cells. They complete their lineage commitment at the DN3 stage during thymic development and ultimately migrate to peripheral blood or tissues[19] (**Fig. 1**). Besides, study of human peripheral blood and postnatal thymus suggests that Vγ9Vδ2 T cells may experience expansion in the periphery.[20]

2.2. Antigen recognition of γδ TCR

Conventional αβT cells recognize their antigens which are peptides presented by MHC molecules via TCR. Vγ9Vδ2 T cells, the predominant subset of γδ T cells, recognize the PAgs produced by bacteria or viruses through nonmevalonate isoprenoid synthesis pathways, such as the high-affinity PAg (*E*)-4-hydroxy-3-methyl-but-2-enyl-pyrophosphate (HMBPP)[21] and endogenous PAgs, such as the lower-affinity PAg isopentenyl pyrophosphate (IPP), which are generated via the mevalonate pathway in the tumor microenvironment.[22] The activation of Vγ9Vδ2 T cells depends on the binding of PAgs and butyrophilin subfamily 3 member A1 (BTN3A1), which induces a conformational change in BTN3A1 and interaction with BTN2A1.[23] Therefore, aminobisphosphonates such as zoledronate (ZOL), which disrupt the mevalonate pathway and cause an accumulation of IPP, or synthetic PAg analogs, such as bromohydrin pyrophosphate (BrHPP) are commonly used to expand Vγ9Vδ2 T cells.[24] In addition, unlike Vγ9Vδ2 T cells, Vδ1 T cells, the major tissue γδ T cells subset, recognize lipid antigen presented by CD1[25,26] and function as naive cells in host defense. Overall, knowledge about γδ TCR remains poorly understood, and the molecular basis involved needs to be elucidated.

3. FUNCTIONS OF γδ T CELLS IN HEMATOLOGICAL CANCERS

3.1. Mechanisms of γδ T cell-mediated killing in hematological malignancies

The antitumor functions of γδ T cells have been demonstrated in vitro and in mouse models (**Fig. 2**). Girardi et al first showed this ability in mice with cutaneous squamous cell carcinoma,

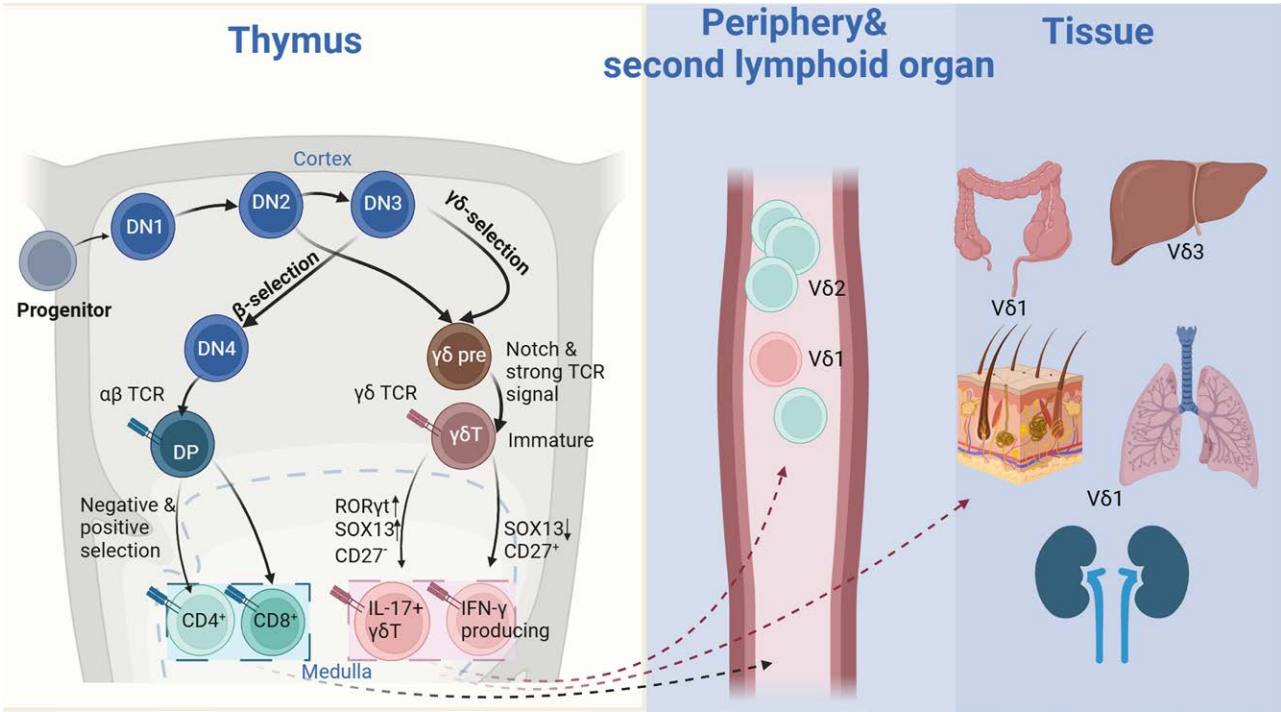

Figure 1. γδ T cell development. The diagram depicts the development of γδ T cell and αβ T cell from bone marrow progenitors. They originate from common thymic precursors and branch from DN3 thymocytes stage. Functional expression of αβ TCR or γδ TCR drives cells into αβ T or γδ T cell lineage. αβ T cells which undergo positive and negative selection are mature and eventually migrate to periphery and second lymphoid organ. While γδ T cells gain IL-17 or IFN-γ-producing properties through different transcriptional factor signal and ultimately migrate to peripheral blood or tissues. IFN-γ = interferon-γ, IL-17 = interleukin 17, TCR = T-cell receptor.

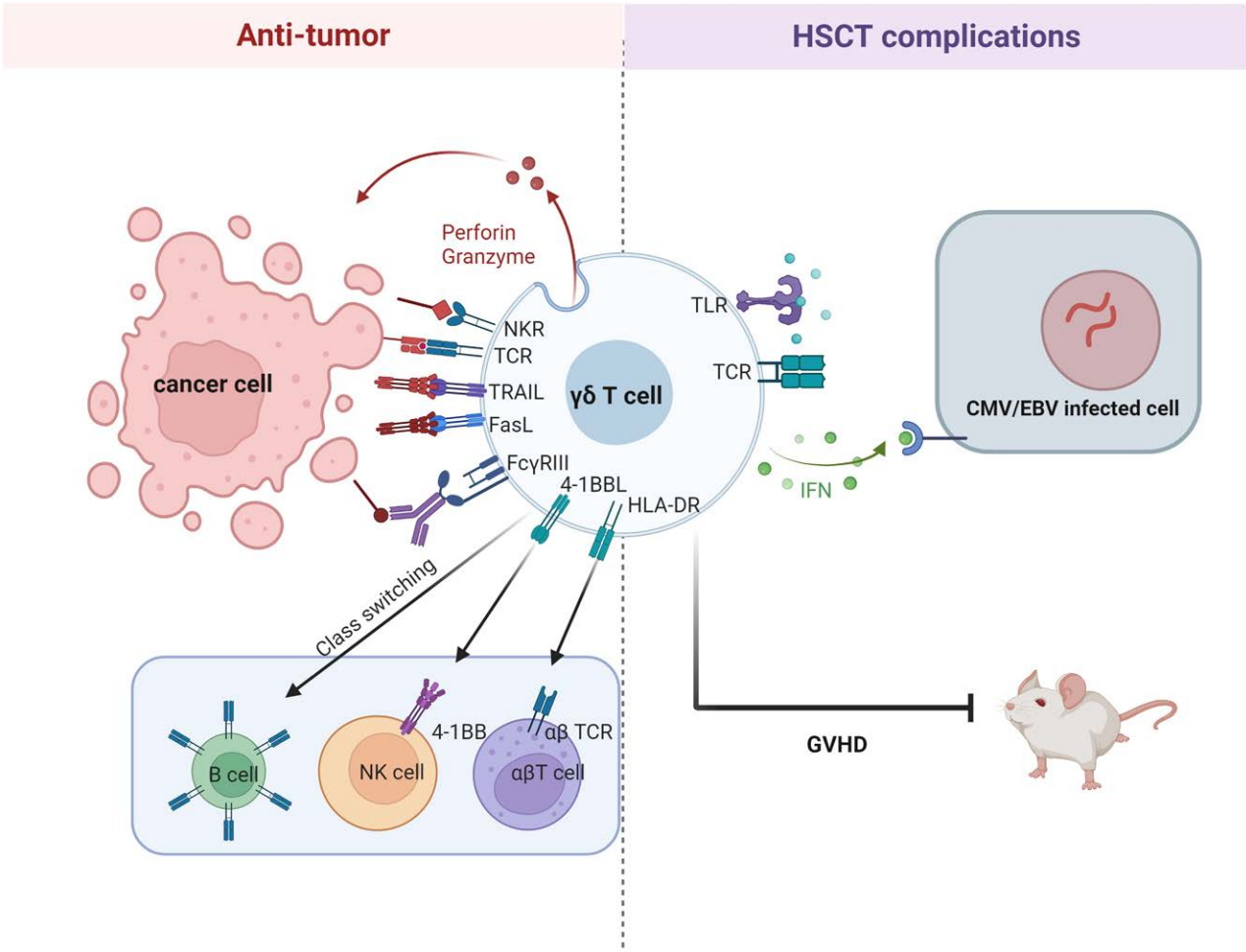

Figure 2. The functions of γδ T cells. Human γδ T cells exhibit potent cytotoxicity against various tumors through multiple mechanisms, such as receptor-ligand interactions (eg, γδ TCR, NKR, TRAIL, and FasL), cytokine secretion (eg, IFN-γ, TNF-α) and release of cytolytic granules (eg, granzyme B and perforin). They can also mediate ADCC against tumor cells. Furthermore, they can modulate anticancer immunity by interacting with other immune cells, such as B cells, NK cells, and αβ T cells. In particular, Vδ2-negative T cells have been shown to play a crucial role in controlling CMV and EBV infections after HSCT, as they can recognize viral particles or infected cells via TLRs, γδTCRs, and NKG2D, and exert antiviral effects by producing IFN or lysing infected cells directly or indirectly through cross-talk with other immune cells. The role of γδ T cells in GvHD is still unclear, but some studies have reported that γδT17 and Vγ4 T cells could ameliorate GvHD in mouse models. ADCC = antibody-dependent cellular cytotoxicity, CMV = cytomegalovirus, EBV = Epstein–Barr virus, FasL = Fas ligand, GvHD = graft-versus-host disease, GZMB = granzyme B, HSCT = hematopoietic stem cell transplantation, IFN-γ = interferon-γ, NKG2D = natural killer group 2-member D, TCR = T-cell receptor, TLR = toll-like receptor, TNF-α = tumor necrosis factor α, TRAIL = tumor necrosis factor-related apoptosis-inducing ligand. Figures are created with Biorender.com.

demonstrating that γδ T cells suppressed cancer development.[27] Subsequently, γδ T cells were shown to effectively lyse various cancer cells, including those from solid tumors and hematological malignancies.[28–30] Furthermore, several clinical trials have confirmed the safety of γδ T cells in adoptive immune cell therapy.[31] γδ T cells recognize cancer cells mainly via γδ TCR and NKR. Therefore, ZOL-pretreated tumor cell lines that accumulate IPP are sensitive to γδ T-cell killing.[32] Gertner-Dardenne et al[33] reported that DNAX accessory molecule-1 (DNAM-1) ligands such as poliovirus receptor (PVR, CD155) and Nectin-2 were more highly expressed in acute myeloid leukemia (AML) blasts and confirmed the TCR- and DNAM-1-dependent cytotoxicity of Vγ9Vδ2 T cells using blocking assays. Moreover, AML blasts could be killed by the perforin and granzyme pathways.[33] Kunzmann's[34] group showed that Vγ9Vδ2 T cells were directly activated by NKG2D by binding with MHC class I chain-related protein A (MICA), and they identified the NKG2D ligand ULBP1 as a significant biomarker to predict sensitivity to Vγ9Vδ2 T-cell killing through comprehensive analysis of primary AML samples.[35] In addition, soluble ULBP4, another NKG2D ligand, was shown to activate Vγ9Vδ2 T cells via both γδ TCR and NKG2D.[36] On the other hand, stress-induced MICA and MHC class I chain-related protein B (MICB) or soluble MIC ligands were also found to be recognized by intestinal epithelial Vδ1 T cells.[37,38] Vδ1 T cells could be induced to express NKp30, NKp44, and NKp46 in a manner dependent on phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling, resulting in increased cytotoxicity against lymphoid leukemia cells and chronic lymphocytic leukemia (CLL), with abundant granzyme B, interferon-γ (IFN-γ) and tumor necrosis factor α (TNF-α) secretion.[30,39] Moreover, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and Fas are involved in the killing activity of Vδ1 T cells against B-CLL cell lines.[40] Notably, Vγ9Vδ2 T cells can mediate cytotoxicity via antibody-dependent cell-mediated cytotoxicity (ADCC), which enhances monoclonal antibody therapy.[41,42] In addition, γδ T cells also mediate antitumor activity by interacting with other immune cells, such as activating natural kill (NK) cells through 4-1BB, assisting antibody class switching of B cells and activating αβ T cells via human leukocyte antigen (HLA)-DR molecules.[7]

γδ T cells have demonstrated significant antitumor activity in various hematologic malignancies, despite these capabilities,

γδ T cells face significant challenges within the tumor microenvironment (TME) that can lead to functional impairment and exhaustion. Continuous exposure to tumor-associated PAgs, such as IPP and HMBPP, drives γδ T cells toward a state of chronic stimulation, ultimately leading to exhaustion.[43] The enhanced mevalonate pathway activity in tumor cells increases the production of PAgs, which overstimulates γδ T cells, diminishing their antitumor efficacy. The immunosuppressive nature of the TME is reinforced by a variety of inhibitory cells, including myeloid-derived suppressor cells (MDSCs), Tregs, and M2-polarized tumor-associated macrophages (TAMs). These cells secrete cytokines such as transforming growth factor-β (TGF-β) and IL-10, which promote the differentiation of γδ T cells into tumor-promoting phenotypes like γδT17 cells and γδTregs, further reducing their antitumor potential.[44,45] Additionally, MDSCs can inhibit IFN-γ secretion by γδ T cells, impairing their cytotoxic functions,[46] while reactive oxygen species (ROS) released by neutrophils can suppress γδ T cell activation and proliferation.[47] In addition, compared to healthy cells, γδ T cells within the TME often exhibit elevated levels of immune checkpoint receptors (ICRs), which contributes to functional impairment and diminished cytotoxicity. The balance between inhibitory and costimulatory signals is critical; excessive inhibitory signaling can shift γδ T cells toward a state of anergy. Notably, immune checkpoints such as programmed death-1 (PD-1), TIM3, Lag-3, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and B and T lymphocyte attenuator (BTLA) are known to prevent proper activation of γδ T cells and driving them toward dysfunction.[48–50] Collectively, negative effects of TME are critical barriers to the efficacy of γδ T cell-based therapies in hematological malignancies and highlights the importance of strategies aimed at modulating the TME to enhance γδ T cell infiltration, survival, and function.

3.2. Exploration of γδ T cell-based cellular therapy in hematological cancers

Adoptive cellular therapy has been extensively explored for cancer therapy. Immune cells such as αβ T cells, NK cells, and genetically modified T cells, including engineered TCR-T cells and chimeric antigen receptor (CAR) T cells, have shown potential as effector cells against hematological cancers but still present various limitations, such as short persistence and unexpected toxicity.[51] Current studies on solid cancers or hematological cancers have indicated that γδ T cells are associated with favorable clinical outcomes for most cancer types,[52–54] suggesting a prognostic value of γδ T cells. However, some distinct protumor phenotypes, such as IL-17$^+$ γδ T cells, are related to unfavorable outcomes and are mainly found in solid cancers.[55] In particular, γδ T cells have emerged as promising products for hematological malignancies therapy.

3.2.1. Leukemia Several clinical reports in the late 1990s suggested the favorable role of γδ T cells after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Lamb et al[56] reported that 43 leukemia patients who received partially HLA-mismatched grafts depleted of αβ T cells had improved disease-free survival (DFS) if they had an increased (≥10%) proportion and number of γδ T cells in the first 6 months. After 3 years of follow-up, they confirmed that these γδ T cells were Vδ1$^+$CD69$^+$ and cytotoxic to K562 cells in vitro. An increased percentage of these Vδ1$^+$ T cells was associated with lower relapse rates and better survival.[57] In a subsequent 8-year study, they extended the clinical trial to 153 patients with acute lymphoblastic leukemia (ALL) or AML. They confirmed that increased percentages of γδ T cells in leukemia patients undergoing αβ T cell-depleted allo-HSCT had an overall survival (OS) and DFS advantage.[58] Similarly, a study of 80 children with acute leukemia who received HLA-haploidentical allo-HSCT with grafts manipulated by αβ T-cell and B-cell depletion[59] and a study of 102 pediatric patients with leukemia who underwent allo-HSCT[60] all showed a positive relation between γδ T cells and improved outcome. These clinical trials indicate that γδ T cells may play an important role in the graft-versus-leukemia (GvL) effect.

Kunzmann et al[61] conducted a prospective clinical trial using ZOL and IL-2 in vivo to expand Vγ9Vδ2 T cells of patients with renal cell carcinoma, melanoma, and AML. They reported a significant increase in the percentage of γδ T cells and production of IFN-γ but no objective responses in solid tumor patients and only 2 (25%) partial remissions (PR) in AML patients, suggesting a limited GvL effect of autologous γδ T cells. In a subsequent trial,[62] 4 refractory hematological malignancy patients received haploidentical family donor peripheral blood mononuclear cells after CD4 and CD8 depletion plus serial ZOL infusions. The researchers observed an elevated number of γδ T cells, and 3 (75%) patients achieved complete remission without GvHD. These trials demonstrated the safety and feasibility of allogeneic γδ T cell-based therapy.

3.2.2. Lymphoma and MM γδ T cells stimulated by aminobisphosphonates such as pamidronate, alendronate, and ibandronate[63] or specific synthetic PAgs[64] in vitro showed specific cytotoxicity against lymphoma and myeloma cell lines. Wilhelm et al[65] enrolled 19 patients with relapsed or refractory low-grade non-Hodgkin lymphoma (NHL) or MM and assessed the in vivo expansion and activity of γδ T cells after pamidronate and IL-2 infusion. They found that only 3 patients (33%) who had a significant increase in the percentage of γδ T cells achieved PR, indicating the antilymphoma and antimyeloma potential of in vivo-expanded and in vivo-activated γδ T cells. Abe's group[66] performed the first adoptive cellular therapy of γδ T cells for MM patients by expanding Vγ9Vδ2 T cells in vitro using ZOL and administering sufficient Vγ9Vδ2 T cells to nine MM patients. The results of this pilot study were disappointing, as none of the patients showed an improved outcome, suggesting a need for novel strategies for γδ T cell-based therapy.

4. γδ T CELLS IN HSCT COMPLICATIONS

4.1. Relationships between γδ T cells and GvHD

GvHD is a major transplant-related complication after allo-HSCT or adoptive cell therapy. The role of γδ T cells in GvHD is controversial. Several clinical studies have suggested that γδ T cells do not affect the onset and exacerbation of GvHD.[56,67,68] In another clinical trial (NCT01810120), 80 children with acute leukemia received allo-HSCT mainly composed of γδ T cells due to αβ T-cell and B-cell depletion, and they showed a lower incidence of acute GvHD (aGVHD) and chronic GvHD (cGVHD), indicating a protective effect of γδ T cells.[59] In line with human data, some preclinical studies confirmed that γδ T cells are not involved in GvHD development.[69,70] Using a murine aGVHD model, Song et al[71] found that a specific subset of γδ T cells, Vγ4 γδT cells, attenuated aGVHD after allo-HSCT by suppressing CD4$^+$ T-cell activation. Similarly, Hu's group[72] generated a novel population of immunoregulatory γδ T cells induced by decitabine, TGF-β1, and other cytokines. These γδ Treg cells inhibited GvHD in a mouse model.[72] The researchers also analyzed the clinical data of patients who underwent allo-HSCT and found a significantly increased number of Foxp3$^+$ γδ Tregs in the non-cGVHD group.[73] Moreover, another subset of IL-17-producing γδ T cells was effective in ameliorating intestinal aGvHD in an aGvHD mouse model by increasing the infiltration of Gr-1$^+$CD11b$^+$ MDSCs into the inflamed intestine.[74] However, some studies suggest that γδ T cells contribute to the pathogenesis of GvHD. In a murine study, γδ T cells were reported

to enhance the allo-stimulatory ability of DCs and exacerbate aGvHD in allogeneic bone marrow transplantation models.[75] Another murine study showed that γδ T cells induced lethal GvHD.[76] Furthermore, in a clinical study, patients who received allogeneic peripheral blood stem cell transplantation were evaluated according to the severity of GvHD, and the researchers found that a higher infusion dose of γδ T cells was associated with more severe aGvHD (aGvHD II-IV).[77] Overall, specific subsets of γδ T cells such as Vγ4 γδT cells, Foxp3$^+$ γδ Tregs, and IL-17-producing γδ T cells are involved in the prevention of GvHD, while some other subsets of γδ T cells participate in the promotion of GvHD. These conflicting studies indicate that more investigations and clinical data are needed to elucidate the relationships between different subsets of γδ T cells and GvHD.

4.2. Crucial roles of γδ T cells in infectious complications after HSCT

Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) infection are common during the reconstitution of immune cells and granulocytes after HSCT. Several clinical studies have suggested that γδ T cells have a protective effect against infection during HSCT.[60,78–80] A study of 102 pediatric patients with leukemia who underwent allo-HSCT showed that patients with increased numbers of γδ T cells had a lower risk of infection than those with low/normal numbers of γδ T cells.[60] Of note, the antivirus functions are limited to Vδ2-negative γδ T cells. Fujishima et al[81] demonstrated that these Vδ1 T cells were cytotoxic against autologous EBV-lymphoblastoid cell lines (LCLs) in vitro. Similarly, patients who received cord blood transplantation exhibited early expansion of Vδ1 T cells in EBV infection settings, and these Vδ1 T cells were differentiated and could lyse EBV-infected cells.[82] TLRs were identified as the predominant recognized receptors of Vδ2-negative γδ T cells as well as γδ TCR and NKG2D receptor pathways,[83] and the antivirus activity depends on chemokine and cytokine such as IFN-γ production. They can also facilitate the lysis of infected cells in indirect ways by interacting with other immune cells.[84] Therefore, the antiviral activity of γδ T cells suggests tremendous potential for the treatment of infectious complications after HSCT.

5. NOVEL STRATEGIES FOR IMPROVING γδ T CELL-BASED IMMUNOTHERAPY

Several novel strategies have been developed to enhance the efficiency of γδ T cell-based immunotherapy. Ongoing clinical trials of γδ T cell-based therapies for hematological malignancies are summarized in Table 1.

One strategy is to use monoclonal antibodies that target BTN3A, which is necessary for activating Vγ9Vδ2 T cells. For example, ICT01, an agonist antibody developed by ImCheck Therapeutics,[85] showed robust cytotoxicity against leukemia cell lines and lymphoma cell line (Daudi), and the first-in-human phase I/IIa trial (EVICTION: NCT04243499) is ongoing, the preliminary data indicate good safety. The EVICTION trial is an open-label Phase I/IIa study that explores ICT01 both as a monotherapy for solid and hematological malignancies and in combination with pembrolizumab for solid tumors. In the Phase I dose-escalation study involving relapsed/refractory hematological malignancies, 26 patients were enrolled, including 24 with AML, 1 with diffuse large B-cell lymphoma (DLBCL), and 1 with follicular lymphoma (FL). All patients had failed prior standard-of-care therapies. ICT01 was administered at doses ranging from 200 μg to 75 mg every 21 days. The primary endpoints were the incidence of treatment-emergent adverse events (AEs) and the disease control rate (DCR), defined as the sum of complete response (CR), CR with incomplete hematologic recovery (CRi), PR, and stable disease (SD). Secondary endpoints included the assessment of circulating γ9δ2 T cells, as well as pharmacokinetic and pharmacodynamic analyses. The reported data showed no dose-limiting toxicities, and a DCR of 30% was observed among the 10 evaluable patients at week 8. Importantly, ICT01 treatment effectively and safely induced the activation and migration of γ9δ2 T cells from the peripheral blood within hours of administration, indicating successful target engagement.[86] Other monoclonal antibodies targeting BTN3A 20.1 also enhanced Vγ9Vδ2 T cell-mediated killing of AML blasts, including those that are poorly sensitive to nitrogen-containing bisphosphonates (N-BPs).[87,88]

Another strategy is to use bispecific antibodies that can simultaneously engage γδ T cells and leukemia antigens. Recently, a unique bispecific antibody that is derived from the linkage of a CD1d-specific single-domain antibody with a Vδ2-TCR-specific single-domain antibody was developed. It engaged Vγ9Vδ2 T cells with NKT cells to target tumor cells that express CD1d, which reduced side effects such as cytokine release syndrome and off-tumor toxicity with high efficacy.[89] In addition, other bispecific anti-CD1d-Vδ2 antibody,[90] anti-Vγ9-CD123 antibody,[91] and anti-CD40-Vγ9Vδ2 T-cell engager[92] exhibited improved cytotoxicity in the treatment of CLL, AML, and MM, respectively.

A third strategy is to use allogenic cell therapy. A phase I clinical trial (NCT03533816) of allogeneic γδ T-cell (INB-100) infusion after HSCT is ongoing.[93] INB-100 is a γδT cell product expanded from haploidentical transplant donors. Patients received haploidentical stem cell transplantation followed by infusion of INB-100 within 7 days post-engraftment. Two dose cohorts were evaluated: 1×10^6 cells/kg and 3×10^6 cells/kg. As of August 12, 2024, the latest clinical trial data released by INBio reports that 10 patients, primarily diagnosed with AML, have been enrolled. The median follow-up period is

Table 1

Ongoing clinical trials for hematological malignancies treatment.

Strategies	Company	Disease	Phase	Clinical trials
Monoclonal antibody				
BTN3A agonist antibody	ImCheck Therapeutics	Hematopoietic/lymphoid cancer	I/IIa	ICT01 (NCT04243499)
Bispecific antibody				
Vγ9TCR-CD1d	Lava Therapeutics	CLL/MM/AML	I/IIa	LAVA-051 (NCT04887259)
Allogeneic γδT cell				
DOT cells	GammaDelta Therapeutics	MRD$^+$AML	I	GDX012 (NCT05001451)
γδ T	IN8bio	AML/CLL/ALL/myelodysplastic syndromes	I	INB-100 (NCT03533816)
γ9δ2 T	Anhui Provincial Hospital	Recurrent hematologic tumors	I	NCT05755854
γδ TCR-T	Gadeta	AML	I	TEG001 (NTR6541)
γδ TCR-T	Gadeta	MM	I	TEG002 (NCT04688853)
CD20.CAR-Vδ1 T	Adicet Bio	B-cell malignancies	I	ADI-001 (NCT04735471)

CAR = chimeric antigen receptor, DOT = Delta one T, TCR = T-cell receptor.

ww19.5 months, with all patients maintaining morphologic CR for over 12 months. Notably, no relapses have been observed among AML patients to date. Additionally, 3 patients with high-risk disease have remained relapse-free for over 3 years, with a median follow-up of 19.5 months. This is significant considering the high risk of relapse in this patient population and the data showed good safety, highlighting the potential of allogeneic γδ T cell therapy to provide long-term durable responses in this challenging patient population.[68] In our transplantation center, a phase I clinical trial (NCT05755854) of allogeneic Vγ9Vδ2 T cells for the treatment of recurrent hematologic tumors is in the recruiting phase. Besides Vγ9Vδ2 T cells, Bruno's group developed a stable clinical-grade protocol for Delta one T (DOT) cell expansion, which has shown efficient leukemia killing in vitro and in vivo without effect on normal leukocytes.[94]

In addition, multiple modified γδ T cells such as CAR-γδ T cells or γδ TCR-engineered αβT cells have been developed and put into clinical trials. For example, CD19-targeted CAR Vγ9Vδ2 T cells for ALL therapy[95] and CD123-directed CAR DOT cells for AML treatment reduced the tumor burden in leukemia mouse models.[96] Moreover, CAR-Vδ1 T cells directed toward CD20, developed by Adicet Bio under the name ADI-001,[97] have been evaluated in phase 1 clinical trial for B-cell malignancies (NCT04735471). The preliminary data showed an encouraging objective response rate (67%) and CR rate (67%) without GvHD.[98] To overcome the limited proliferation and diversity of Vγ9Vδ2 T cells, Johanna et al[99] established a novel product called TEGs, which combined a defined γδ TCR with αβ T cells. The first-in-human phase I trial of TEG001 (NTR6541) in patients with primary refractory or relapsed AML is ongoing. Moreover, several TEGs (NCT04688853) have been confirmed to have improved efficacy and safety for leukemia treatment and B-cell malignancies.[100,101]

6. CONCLUSIONS AND PERSPECTIVES

γδ T cells are a unique subset of lymphocytes with both innate and adaptive features. They can recognize and eradicate various hematological malignancies through different mechanisms, modulate other immune cells, and enhance their antitumor activity. Moreover, γδ T cells have potent antiviral functions after HSCT, which may improve the outcome of patients with hematological malignancies. However, the clinical application of γδ T cells presents many challenges, such as low frequency in peripheral blood, heterogeneity of different subsets, and immunosuppression by the TME. Exploiting distinct subtypes or differentiation stages of γδ T cells may maximize their function in cell therapy. Pizzolato et al[102] performed single-cell RNA sequencing (scRNA-seq) of human γδ T cells and found that Vδ1 and Vδ2 T cells resemble NK and $CD8^+$ T cells, respectively, according to their single-cell transcriptomes. In a recent study, Vδ1 and Vδ3 subsets were demonstrated that contribute to the response to immune checkpoint blockade therapy in patients with HLA-class-I-defect colon cancers, which underline the potential of γδ T cells in cancer immunotherapy.[103] Second, further studies are needed to optimize the strategies for γδ T-cell expansion, activation, and infusion, such as using optimized molecule drugs, antibodies, or CARs. Additional clinical trials should be conducted to evaluate the safety and efficacy of γδ T cell-based therapy in different hematological malignancies and HSCT settings. Third, combining γδ T cells with traditional anticancer drugs may be beneficial for cancer therapy. Some studies have shown that dasatinib,[104] ibrutinib,[105] and LBH589 (a pan-histone deacetylase inhibitor)[106] can enhance the cytotoxic capacity of γδ T cells.

In conclusion, γδ T cells represent a promising immunotherapeutic tool for hematological malignancies that warrants further investigation.

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