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State of the CAR-T: Risk of Infections with Chimeric Antigen Receptor T-Cell Therapy and Determinants of SARS-CoV-2 Vaccine Responses

Juliet Meir[1], Muhammad Abbas Abid[2], Muhammad Bilal Abid[3,*]

[1] Department of Medicine, Westchester Medical Center, Valhalla, New York
[2] Department of Hematopathology & Microbiology, The Aga Khan University Hospital, Karachi, Pakistan
[3] Divisions of Infectious Diseases and Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

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A B S T R A C T

Chimeric antigen receptor T cell (CAR-T) therapy has shown unprecedented response rates in patients with relapsed/refractory (R/R) hematologic malignancies. Although CAR-T therapy gives hope to heavily pretreated patients, the rapid commercialization and cumulative immunosuppression of this therapy predispose patients to infections for a prolonged period. CAR-T therapy poses distinctive short- and long-term toxicities and infection risks among patients who receive CAR T-cells after multiple prior treatments, often including hematopoietic cell transplantation. The acute toxicities include cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. The long-term B cell depletion, hypogammaglobulinemia, and cytopenia further predispose patients to severe infections and abrogate the remission success achieved by the living drug. These on-target-off-tumor toxicities deplete B-cells across the entire lineage and further diminish immune responses to vaccines. Early observational data suggest that patients with hematologic malignancies may not mount adequate humoral and cellular responses to SARS-CoV-2 vaccines. In this review, we summarize the immune compromising factors indigenous to CAR-T recipients. We discuss the immunogenic potential of different SARS-CoV-2 vaccines for CAR-T recipients based on the differences in vaccine manufacturing platforms. Given the lack of data related to the safety and efficacy of SARS-CoV-2 vaccines in this distinctively immunosuppressed cohort, we summarize the infection risks associated with Food and Drug Administration-approved CAR-T constructs and the potential determinants of vaccine responses. The review further highlights the potential need for booster vaccine dosing and the promise for heterologous prime-boosting and other novel vaccine strategies in CAR-T recipients.

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INTRODUCTION

Chimeric antigen receptor T-cell (CAR-T) therapy, using autologous T-cells redirected toward a tumor-specific antigen, is a useful treatment modality for patients with relapsed/refractory (R/R) hematologic malignancies [1–3]. The engineered T-cells are transduced with a CAR molecule consisting of an antigen recognition single-chain variable fragment (scFv), a transmembrane domain, and an intracellular signaling domain, CD3ζ. The intracytoplasmic and transmembrane portions of a second-generation CAR T-cell contain signaling domains of costimulatory receptors involved in T-cell activation and durability, including CD3ζ, CD28, 4-1BB, ICOS, and OX40. Later-generation CAR T-cell constructs may contain multiple signaling domains that determine durability, eventual CAR T-cell fate, and metabolism independent of major histocompatibility complex (MHC) restrictions [2].

As of this writing, the US Food and Drug Administration (FDA) has approved several CAR-T constructs directed against CD19 and B-cell maturation antigen (BCMA). These include tisagenlecleucel (tisa-cel; Kymriah) for the treatment of R/R acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL), axicabtagene ciloleucel (axi-cel; Yescarta), and lisocabtagene maraleucel (liso-cel; Breyanzi) for treating R/R DLBCL and other lymphomas that share similar histopathological features, and brexucabtagene autoleucel (brex-cel; Tecartus) for treating R/R mantle cell lymphoma (MCL). More recently, idecabtagene vicleucel (ide-cel; Abecma), directed against BCMA, received FDA approval for the treatment of R/R multiple myeloma (MM) [4–9].

Although CAR-T therapy prolongs the survival of patients with R/R diseases, the associated on-target off-tumor toxicities, particularly infections, limit the effective utilization of

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*Correspondence and reprint requests: Muhammad Bilal Abid, Divisions of Infectious Diseases and Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Hub for Collaborative Medicine, 8701 Watertown Plank Road, Milwaukee, WI 53226

E-mail address: bilal_abid@hotmail.com (M.B. Abid).

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this curative therapy. CAR-T poses distinctive short- and long-term toxicities and infection risks among patients who receive CAR-T after multiple prior treatments, often including hematopoietic cell transplantation (HCT). CAR-T construct, signaling domains, cytokine release syndrome (CRS), neurotoxicity, and peri-CAR-T interventions confer risk of unique infections in the early period. The long-term B-cell depletion, hypogammaglobulinemia, and cytopenia further predispose patients to severe infections and abrogate the remission success achieved by the living drug.

RISK OF INFECTIONS IN GENERAL WITH CAR-T THERAPY

The infection-related data reported thus far are limited to CD19-targeted CAR-T. In a single-center retrospective study, examining 85 axi-cel recipients with large B-cell lymphoma (LBCL) who maintained remission post-CAR-T therapy, 37% of patients developed infections by day+30, of which 13% were severe. Severe infections were associated with CRS, neurotoxicity, tocilizumab and corticosteroid use, and bridging therapy on univariate analysis [10]. The general risks of infection with CAR-T therapy are further discussed at length in the section below titled "INFECTION RISK IN RECIPIENTS OF CAR-T IMMUNOTHERAPY."

COVID-19 OUTCOMES IN CELLULAR THERAPY RECIPIENTS

As of August 1, 2021, SARS-CoV-2 has infected more than 200 million people and caused more than 4 million deaths globally. Patients with cancer are at a particularly higher risk, and those with hematologic malignancies are at the greatest risk of severe COVID-19 and mortality (13% to 39%) [11–17]. HCT and CAR-T recipients are at an even higher risk [18]. A recent study from the Center for International Blood and Marrow Transplant Research registry examining 318 HCT recipients showed a mortality rate of 30% at 30 days after the development of COVID-19. Among allogeneic HCT (alloHCT) recipients, increased mortality risk was associated with age >50 years, male sex, and development of COVID-19 within 1 year of transplantation. Among autologous HCT (autoHCT) recipients, patients who underwent HCT for lymphoma had a higher mortality risk than patients with MM [19]. In addition, lymphopenia (defined as absolute lymphocyte count <300/μL) at the time of COVID-19 diagnosis was associated with a higher mortality risk among HCT survivors. Other studies have shown similarly higher mortality among HCT recipients, with increasing age, presence of active graft-versus-host disease, and development of COVID-19 early after HCT as predictors of mortality [15–17].

In a retrospective study from Italy examining 82 HCT recipients who developed COVID-19, death occurred in 33% of autoHCT recipients and in 35% of alloHCT recipients [15]. Older age, progressive disease status, and diagnosis of acute myelogenous leukemia, non-Hodgkin lymphoma (NHL), or plasma cell neoplasms were associated with inferior survival. The Spanish cohort reported a 45-day overall mortality rate of 17% in 65 alloHCT recipients and 18% in 58 autoHCT recipients [20]. Age >70 years and hypertension were associated with an increased risk of mortality. In a study from New York, that examined 77 patients, the clinical outcomes were more favorable, with 78% overall survival at 30 days [16]. Notably, the alloHCT cohort in that study included only a few patients with active graft-versus-host disease.

The study from New York also included 5 patients with B-cell NHL (B-NHL), who had received CAR-T products directed against CD19, including 4 with axi-cel and 1 with tisa-cel [16]. In another case report, a 73-year-old patient with R/R MM developed severe COVID-19 12 days after receiving CAR-T therapy targeting BCMA [21]. The patient developed persistent viremia for >2 months and eventually died. Postmortem sequencing revealed viral evolution with multiple sequence variants within the host concurrent with significantly diminished humoral and cellular immune responses. Another study that included 2 CAR-T recipients in a cohort of 20 cancer patients confirmed profound immunosuppression and prolonged viral shedding and detected viable virus by cell culture [22]. Another study from the Dana-Farber Cancer Institute examined outcomes in 127 cellular therapy patients treated during the initial COVID-19 surge, including 27 CAR-T recipients. During the study period, 1 patient with DLBCL contracted COVID-19 at 51 days after receiving tisa-cel and died from COVID-19-related complications 121 days after CAR-T infusion [23].

OVERVIEW OF B CELL DEVELOPMENT

The risk for infectious pathogens is likely associated with tumor-associated antigen (TAA) and the stage of differentiation at which the antigens are expressed on B-cells. B-cell development begins in the liver, where stromal cells provide cytokines and chemokines to differentiate hematopoietic stem cells into common lymphoid progenitors [24]. With the aid of transcription factors, E2A, and early B-cell factor, common lymphoid progenitor cells differentiate into pro-B-cells [25]. Pro-B-cells then undergo heavy and light chain rearrangement, leading to IgM-expressing immature B-cells [26]. These immature B-cells migrate from bone marrow to spleen and differentiate into mature B-cells, which then differentiate into plasma cells (PCs). Follicular helper T-cells activate B-cells to differentiate into short-lived PCs or enter the germinal center to differentiate into PCs or memory B-cells. These germinal center PCs migrate to the bone marrow to produce specific PCs [27].

CD19 AND BCMA – ANTIGEN PRODUCTION AND ROLE IN IMMUNITY

Two vital antigens are expressed on the B-cell surface during the differentiation process. The B-lymphocyte antigen CD19 is a transmembrane protein expressed in follicular dendritic cells (DCs) and all B lineage cells except PCs. CD19 acts as an adaptor protein to recruit cytoplasmic signaling proteins to the membrane and functions within the CD19/CD21 complex to decrease the threshold for B-cell receptor signaling pathways. Owing to its expression on the cell surface of all B-cells, CD19 is a biomarker for B-cell development, as well as for the diagnosis and treatment response of B-cell hematologic malignancies. It also serves as a target for antileukemia and lymphoma immunotherapies.

BCMA, also known as tumor necrosis factor receptor superfamily member 17 (TNFRSF17), is a protein encoded by the *TNFRSF17* gene. BCMA is expressed on B-cells in the interfollicular region of the germinal center and is preferentially expressed in mature B lymphocytes and on MM cells [28,29]. It plays a significant role in the maturation and differentiation of B-cells into PCs, and its expression is essential for the survival of long-lived PCs [29,30]. Several studies have demonstrated BCMA expression on differentiated PCs in normal lymphoid tissue (bone marrow, lymph nodes, spleen, and tonsils) and lack of expression on naïve B-cells and other hematopoietic cells, including neutrophils, macrophages, and T-cells. In addition, BCMA is consistently expressed on malignant PCs, with only limited distribution in normal tissue [31–34]. Up-regulation of BCMA also correlates with disease burden and

prognosis in MM and serves as a target for antimyeloma immune-engaging platforms [31,35].

CELL SURFACE ANTIGENS AND RISK OF BACTERIAL AND VIRAL INFECTIONS

CD19 is expressed selectively on earlier-stage B-cells and follicular DCs and plays a role in antigen-independent development and immunoglobulin activation of B-cells [36–40]. Unlike BCMA, however, terminal PCs lose CD19 expression [38,39]. Malignant PCs also lack surface CD19 expression [41]. Studies have demonstrated only a weak T cell-dependent humoral response in CD19-deficient mice and humans, owing to the lack of expression of CD19 on PCs [38,42]. Other studies have shown that a mutation in the *CD19* gene leads to adequate differentiation of precursor and early B-cells but decreases in memory B-cells, resulting in hypogammaglobulinemia [37]. With the depletion of CD19 on nonmalignant cells, CD19-directed CAR-T recipients could be at higher risk for bacterial infections, particularly in the initial post-CAR-T period.

The globally compromised immune repertoire with BCMA-directed CAR-T could lead to preferentially more viral infections and due to intracellular pathogens compared with more bacterial infections with CD19-directed CAR-T. Thus, patients with R/R MM receiving anti-BCMA CAR-T therapy could be at a notably higher risk of developing severe COVID-19. Consequently, routine reassessment of immune response and booster doses may be necessary.

Although limited, some data are available on BCMA expression in neurons, mainly in the basal ganglia and the cerebellum [43,44]. Although the findings require validation and proof-of-concept, ongoing clinical trials of anti-BCMA CAR-T and bispecific T-cell engagers will highlight any non-T-cell-mediated neurotoxicity related to BCMA expression. Expectedly, a higher level of clinical suspicion should be maintained for the risk of central nervous system infections with anti-BCMA therapy.

HUMORAL AND CELL-MEDIATED IMMUNITY TO VIRAL INFECTIONS

An intricate balance of humoral and cell-mediated immunity protects against viral infections. Humoral immunity is provided by the B-cells that produce antibodies. The protective antibodies neutralize virus and prevent its entry into host cells. Protective immunity is rendered by neutralizing antibodies, the potency and concentration of which are quantified as the titer required to neutralize 50% of viral plaques in an immunoassay (50% inhibitory dilution [ID_{50}]). The neutralizing titers are then correlated with clinical outcomes; for instance, a hemagglutination inhibition titer of 1:40 is thought to provide 50% protection from influenza infection [45].

Macrophages and cytotoxic ($CD8^+$) T-cells eliminate virus-infected cells and constitute cell-mediated immunity [46]. Helper ($CD4^+$) T-cells activate B and $CD8^+$ T-cells. $CD4^+$ T-cell subsets, including Th1 and Th2, orchestrate phagocytosis, cell-mediated immunity, and allergic-type inflammation. Antigen-specific memory B and T-cells persist and provide memory to prevent future infections [47].

In a viral infection, the innate immune response is initiated by antigen-presenting cells, such as macrophages and DCs, which present processed viral peptides to major histocompatibility complex molecules and prime naïve antigen-specific T-cells in the secondary lymphoid tissues. Costimulatory molecules and cytokines aid optimal T-cell priming. Immune correlates of protection against SARS-CoV-2 are being explored, and the existing data indicate that a combination of humoral and cell-mediated immunity to SARS-CoV-2 is essential for preventing severe and recurrent illness. Studies have shown robust cell-mediated immune responses in immunocompetent individuals after the SARS-CoV-2 vaccine. The mRNA vaccine has been shown to produce $CD4^+$ and $CD8^+$ T-cell responses, including Th1 cell responses and abundant expression of IFN-γ and IL-2 [48,49]. Similarly, a study examining the recombinant adenovirus vector SARS-CoV-2 vaccine reported increased expression of IFN-γ without an IL-4 response, favoring a Th1 cell response [50]. The kinetics and robustness of immune response to COVID-19 in immunocompetent patients have been reviewed further elsewhere [18,51].

INFECTION RISKS IN RECIPIENTS OF CAR-T IMMUNOTHERAPY

Although there is a dearth of data related to COVID-19 outcomes in CAR-T recipients, there is more evidence related to CAR-T therapy-related infection risk in general. The risk of infections associated with CAR-T depends on various patient- and disease-related factors. The use of a lymphodepletion (LD) chemotherapy regimen, the interval between cell collection and infusion, bridging therapy, CAR T-cell dose, fresh versus cryopreserved cells, single versus fractionated dosing, signaling and costimulatory domains, TAA (CD19 versus BCMA), and duration of lymphopenia and hypogammaglobulinemia are some of the key factors that may confer an increased risk of infections (Figure 1, Table 1) [2,10,52-61]. In addition, CAR-T recipients are more likely to be older (immunosenescence) with a suboptimal performance status, a higher comorbidity burden, and are more likely to have undergone multiple lines of treatment before CAR-T therapy.

Risk of Infections with Signaling Domains CD28 and 4-1BB

The 2 most frequently used signaling domains of costimulatory receptors in modern CAR-T constructs are CD28 and 4-1BB. CD28-based CAR T-cells elicit a robust initial proliferative response and yield effector memory T-cells, whereas 4-1BB costimulation induces a slower and progressive response and endow CAR T-cells with enhanced persistence and central memory differentiation [62–65]. Theoretically, CD28-based CAR-T constructs confer a higher risk of and more frequent and severe CRS compared with 4-1BB-based CAR-T constructs; however, the toxicities need to be compared in head-to-head prospective analyses, as varying CRS grading and treatment algorithms were used in the pivotal trials that led to FDA approval of CD28- and 4-1BB-based CAR-T products. The data from pivotal clinical trials for FDA-approved CAR-T constructs are provided in Table 2.

LD Chemotherapy Regimen and Intensity

In vitro studies have demonstrated that cyclophosphamide (Cy)-based conditioning chemotherapy improves the efficacy and expansion of adoptively transferred tumor-infiltrating lymphocytes [66]. The LD or conditioning regimen decreases the tumor burden and modifies the tumor microenvironment to eliminate the immunosuppressive elements and make it conducive to CAR expansion and persistence of T-cells [67,68]. Several mechanisms prime the tumor microenvironment and alter the tumor phenotype. Decreased production of certain metabolites in tumor cells, increased expression of costimulatory molecules, down-regulation of immunosuppressive elements such as regulatory T-cells and myeloid-derived suppressor cells, and eradication of homeostatic cytokine sinks result in greater availability of IL-2, IL-7, and IL-15 [66,69-71].

The addition of fludarabine (Flu) to Cy has been associated with improved anti-CD19 CAR-T expansion and persistence

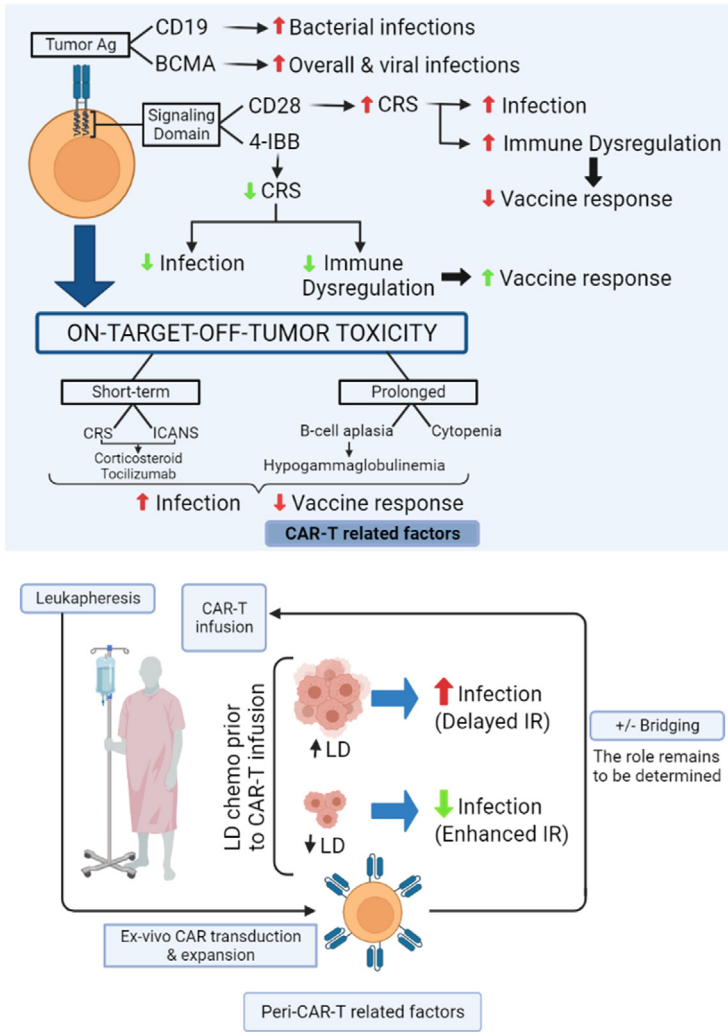

Figure 1. Predictors of infections and SARS-CoV-2 vaccine responses in CAR-T recipients: Figure 1, panel A: CAR-T-related factors: Immunity to SARS-CoV-2 is conferred by intricate crosstalk of both antibody and T-cell responses. Prolonged B-cell aplasia, hypogammaglobulinemia, and prolonged cytopenia predispose CAR-T recipients to severe infections. CD28-based CAR-T constructs likely confer a higher risk or more frequent and severe CRS as compared to 4-1BB-based CAR-T constructs and hence a higher incidence for infections. CAR-T targeting CD19 likely results in more bacterial infections, whereas viral infections commonly occur following BCMA-directed CAR-T. Cumulative dosages of corticosteroids and tocilizumab further increase the infection risks and negatively impact vaccine responses. Figure 1, panel B: Peri-CAR-T related factors: The risk of infections and humoral and cellular response to SARS-CoV-2 vaccine with CAR-T depends upon several patient-, disease-related factors, and interventions performed around the period of CAR-T infusion. These include lymphodepletion chemotherapy regimen, the interval between cell collection and infusion, bridging therapy, CAR T-cell dose, and duration of lymphopenia and hypogammaglobulinemia.

and better clinical outcomes compared with non-Flu-containing LD regimens [72]. Thus, FluCy is the most widely used LD chemotherapy, albeit with varying dosing regimens. LD chemotherapy before CAR-T therapy impacts the efficacy, toxicity, and persistence of infused CAR-T cells; however, the optimal regimen and intensity remain unclear. A higher intensity LD regimen may predispose patients to a higher risk of infections. Clinical data showing a direct association of LD chemotherapy dose with infections are limited but evolving. A recent preliminary report of a prospective trial examining the safety and efficacy of an off-the-shelf CD19-targeting allogeneic CAR-T construct given to 13 patients with R/R NHL showed considerably higher rates of infections and CRS-related adverse events in patients who received an escalated LD regimen compared with those who received a standard LD regimen. Two of 7 patients who received escalated LD developed grade ≥3 infections, compared with none of the 6 patients with infections in the standard LD group [61].

CRS as a Risk Factor for Infections

Mechanisms of CRS conferring a higher risk of infections

The FDA-approved second-generation CAR-T constructs differ primarily in their costimulatory domains, either 4-1BB-based (tisa-cel, liso-cel, and ide-cel) or CD28-based (axi-cel and brex-cel) CARs [4–9]. This confers a differential risk of CRS, particularly of severe CRS. The immune dysregulation associated with CRS has been linked to the risk of infections. Although the exact mechanisms that incite and perpetuate CRS remain to be elucidated, the hypercytokinemia related to robust expansion of CAR T-cells may lead to immune paralysis, tissue damage, and disruption of the mucosal barrier [73–75].

The production of IL-6 is thought to be critical to the development of CRS. IL-6 signaling is positively correlated with the production of other proinflammatory cytokines and chemokines [75]. In addition, IL-6 activates the differentiation of monocytes and macrophages, inhibits regulatory T-cells, and attracts other immune cells, potentially amplifying CRS [76,77]. Furthermore, severe CRS has been shown to delay

Table 1
Patient-, Disease-, and CAR-T Therapy-Related Factors Potentially Associated with the Risk of Infections*

Factors to be considered	Additional notes	Reference
Disease/tumor-related factors		
Disease status at CAR-T infusion	⇩ risk with disease in remission (likely)	
Prior lines of therapy	⇧ risk with greater prior lines of treatment (cumulative immunosuppression)	1
Prior HCT	Dependent upon the number/types of prior HCT, donor type, allograft source, conditioning regimen, and intensity	2
Interval between prior HCT and CAR-T	⇩ risk with longer interval (likely)	
Time from diagnosis to CAR-T	⇩ risk with longer interval (likely)	
CNS status at diagnosis or at time of CAR-T	⇧ risk with CNS involvement (likely)	
ALL		3
Cytogenetics risk	⇧ risk with high-risk cytogenetics (likely)	
MRD status at CAR-T infusion	⇩ risk with MRD-negative disease (likely)	
B-NHL		
Size of largest nodal mass at the time of CAR-T	⇧ risk with bulky disease	4
LDH at the time of CAR-T (or prior to LD)	⇧ risk with a higher disease burden	4
MM		1
Cytogenetics risk	⇧ risk with high-risk cytogenetics (likely)	
ISS stage	⇧ risk with advanced stage and aggressive disease (likely)	
Immunochemical subtype	⇧ risk with IgM immune paresis (likely)	
Number and lines of therapy < CAR-T	⇧ risk with greater prior lines of treatment (cumulative immunosuppression)	1,5
Type of prior treatment (PI, IMID, mAb, SINE)	⇧ risk with PIs; ⇧ theoretical risk with SINEs	6,7
Patient-related factors		
Age at the time of CAR-T infusion	⇧ risk with older age	8
Race/ethnicity	⇧ risk with ethnic minorities (AA, Hispanics, PI)	9,10
BMI	⇧ risk of infections with higher BMIs	11,12
KPS	⇧ risk with poor performance status	13
HCT-CI (or comorbidities)	⇧ risk with higher burden of comorbidities	14
CAR-T related factors		
Time from cell collection to CAR-T infusion	⇩ risk with shorter interval between apheresis and CAR-T infusion (likely)	
Prolonged cytopenia	⇧ risk with duration and depth of cytopenia	5,15-17
Lymphodepleting chemotherapy:	⇧ risk with Cy-based LD chemotherapy (demonstrated in the setting	2,4,18-22

(*continued*)

FluCy, Bendamustine, other	of haploHCT)	
Dose of CAR T-cells	⇧ risk with higher dose of CAR T-cells	3
Dose of LD chemotherapy	⇧ risk with higher dose of LD chemotherapy	23,24
Bridging chemotherapy	⇧ risk with bridging therapy (rapidly progressive disease; cumulative immunosuppression)	25,26
CAR-T target antigen (CD19 vs BCMA)	⇧ risk for bacterial with CD19 and viral (+ overall) infections with BCMA. • Greater overall risk for infections with BCMA. • diminished vaccine responses with BCMA.	1,27,28
Signaling domain (CD28 vs 4-1BB)	⇧ risk with CD28 (driven by a higher risk of CRS)	
CRS (severity)	⇧ risk with more severe CRS	3,13,25,29
Infection prior to CAR-T	⇧ risk with infections history of infections prior to CAR-T	13
Hypogammaglobulinemia, post-CAR-T	⇧ risk with duration and depth of hypogammaglobulinemia	1,2
Use of steroids and tocilizumab	⇧ risk due to cumulative immunosuppression	1,13,25,30,31
Year of CAR-T infusion	⇩ risk with more recent CAR-T (due to improved supportive care and antimicrobial prophylaxis) (likely)	

*Variables that have been shown to independently impact the risk of infection in CAR-T setting are referenced. The remaining factors are extrapolated from the allogeneic HCT data.

Abbreviations: CAR-T, chimeric antigen receptor T-cells; CNS, central nervous system; HCT, hematopoietic cell transplantation; ALL, acute lymphoblastic leukemia; MRD, measurable residual disease; B-NHL, B-cell non-Hodgkin's lymphoma; LDH, lactate dehydrogenase; LD, lymphodepletion; MM, multiple myeloma; ISS, international staging system; IgM, immunoglobulin M; PI, proteasome inhibitor; IMiD, immunomodulatory agent; mAb; monoclonal antibody; SINE, selective inhibitor of nuclear export; BMI, body mass index; KPS, karnofsky performance score, HCT-CI, hematopoietic cell transplantation comorbidity index; FluCy, fludarabine and cyclophosphamide; HaploHCT, haploidentical HCT; BCMA, B-cell maturation antigen; CRS, cytokine release syndrome.

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neutrophil engraftment, which may predispose to infections [75,78]. Coupled with the compounded use of immune modulators used for its treatment, such as corticosteroids and IL-6 blockade, the immune dysregulation after severe CRS also may impact long-term responses to vaccines [59,79,80].

A single-center study examining the clinical presentation and biomarkers of severe CRS in 133 adult patients who received CD19$^+$ CAR-T therapy showed that 70% of patients developed CRS. Multivariable analysis identified high marrow tumor burden, LD using Cy and flu, higher CAR T-cell dose, thrombocytopenia before LD, and manufacturing of CAR T-cells without selection of CD8$^+$ central memory T-cells as independent predictors of CRS. Severe CRS was characterized by hemodynamic instability, capillary leak, and consumptive coagulopathy. Endothelial dysfunction coincided with severe CRS and was accompanied by high serum biomarkers and endothelium-activating cytokines, such as IL-6 and IFN-γ [81].

Clinical data related to higher infection risk with CRS

CRS severity has been shown to be associated with an increased risk for infections in several studies. A study examining infection density and pretreatment and post-treatment risk factors for infection within the first 3 months among 133 CD19$^+$ CAR-T recipients showed a higher infection density in the first 30 days than between days 31 and 90. Within the first 30 days, bacterial infections were the most common (23% of patients), followed by viral (17%) and fungal (3%) infections. Although ALL, more previous lines of treatment, and higher CAR T-cell doses were associated with a higher infection density, CRS was the sole risk factor independently associated with infections. In addition, 46% of the patients had hypogammaglobulinemia (IgG $<$400 mg/dL) by day+90 [80]. Similar findings have been reported in patients who received CD19$^+$ CAR-T therapy and developed CRS after T-cell infusion. Park *et al.* [59] showed that CRS grade $\geq$3 was significantly associated with infection risk, particularly bloodstream infections, in a phase-I trial of CD19$^+$ CAR-T therapy in 53 patients with B-cell ALL. Within 30 days of CAR-T infusion, 42% of the patients experienced 26 infections (30% bacterial, 10% viral, and 8% fungal).

The costimulatory domain differed in the 2 aforementioned studies, with 4-1BB in the former study and CD28 in the latter. Other studies also have identified severe CRS, prior HCT, LD chemotherapy regimen, and hypogammaglobinemia as risk factors for subsequent infections with CAR-T [18,52,53,57,58]. Another study examining delayed infections in 60 patients with DLBCL treated with CD19-directed CAR-T also showed that bacterial infections were the most frequent. The cumulative incidence of overall, bacterial, viral, and fungal infections at 1 year were 63%, 57%, 45%, and 4%, respectively [53]. The use of systemic corticosteroids for the management of CRS or immune effector cell-associated neurotoxicity syndrome (ICANS) was shown to be independently associated with an increased risk of infections [53].

CRS in other cellular therapy also confers a higher risk of infection

CRS developing after haploidentical cell transplantation (haploHCT) also has been associated with infections. A single-center study including 78 consecutive adult haploHCT recipients found that severe CRS developing after post-transplantation cyclophosphamide-based haploHCT was independently associated with an increased incidence of infections [78]. The development of severe CRS is associated with a significantly increased risk of nonrelapse mortality, likely driven by increased infections [82].

Hypogammaglobulinemia and Risk of Infection with CAR-T Therapy

CAR-T therapy results in the depletion of normal CD19-bearing cells. The associated hypogammaglobulinemia can be considerably prolonged, predisposes to infections, and impacts outcomes of CAR-T therapy [5,52,53,58,59,80,83]. Furthermore, the durability and response rate to CAR-T correlate with B-cell aplasia. With increasingly sophisticated CAR-T constructs, that harness multiple signaling domains and target multiple TAAs, prolonged B cell aplasia is likely to be an unavoidable, long-term complication in CAR-T recipients for the foreseeable future [2,4,5,7,18,84,85]. However, the incidence and duration of hypogammaglobulinemia as a function of TAA, and its impact on infections and survival and outcomes, have not yet been examined systematically.

CAR T-cell persistence results in delayed B-cell aplasia; hence, hypogammaglobulinemia may be more profound in patients with R/R B-cell ALL treated with tisa-cel than in patients with R/R DLBCL treated with tisa-cel or axi-cel. IgG starts to decrease as early as 1 month after CAR T-cell infusion and can remain low for several years [56,57,84]. In clinical practice, CAR-T recipients often exhibit hypogammaglobulinemia for prolonged periods and develop infectious complications [52,53,58]. The existing data are limited to small, single-center studies and are conflicting in correlating hypogammaglobulinemia with distinctive infections. Several studies have reported that an IgG level $<$400 mg/dL, both pre- and post-CAR-T infusion, is associated with a higher risk of infection. A single-center study evaluating 163 CAR-T recipients identified hypogammaglobulinemia as the most commonly occurring late effect (i.e., event presenting and/or persisting beyond 90 days post-CAR-T infusion) [55]. However, another study in 8 CAR-T recipients suggested a B cell-independent mechanism for the development of long-term humoral immunity. Analysis of bone marrow biopsies after CD19-directed CAR T-cells showed a persistence of antibody-secreting memory PCs for at

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Table 2
Efficacy and on-Target, off-Tumor Toxicities with Approved CAR-T Constructs

CAR-T Construct	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel	Brexucabtagene autoleucel	Idecabtagene vicleucel	Ciltacabtagene autoleucel [*,†]
Abbreviation / commercial product	(tisa-cel/ Kymriah)	(axi-cel/Yescarta)	(liso-cel Breyanzi)	(brex-cel/Tecartus)	(ide-cel/Abecma)	cilta-cel
Clinical trial	JULIET (DLBCL) [5] ELIANA (ALL) [4]	ZUMA-1 [7]	TRANSCEND NHL 001 [9]	ZUMA-2 [6]	KarMMa [8]	CARTITUDE-1 [98]
Study phase	2	2	1	2	2	1b/2
Target antigen	CD19	CD19	CD19	CD19	BCMA	BCMA (2 epitopes)
Costimulatory domains	4-1BB	CD28	4-1BB	CD28	4-1BB	4-1BB
Approved indication	R/R ALL in pediatric and young adults; adult R/R DLBCL	Adult R/R LBCL	Adult R/R LBCL (including DLBCL), high-grade BCL, PMBCL, FL 3B	Adult R/R MCL	RRMM	RRMM
CRS, %	DLBCL: 58[‡] ALL: 77	93[§]	42[§]	91[§]	84[§]	95[#]
Grade ≥3 CRS, %	DLBCL: 22[‡] ALL: 47	13[§]	2[§]	15[§]	5[§]	4[#]
ICANS, %	DLBCL: 21[¶] ALL: 40	64	30	63	18	21[#]
Grade ≥ 3 ICANS, %	DLBCL: 12[¶] ALL: 13	28	10	31	3 grade 3	10[#]
Infections (any grade), %	DLBCL: 39 ALL: 43	35 (febrile neutropenia)	NR	32	69	58
Infections (grade ≥3), % (n/N)	DLBCL: 20 ALL: 24	31 (febrile neutropenia)	12	3 (2/74)	22	20
Sepsis, % (n/N)	NR	NR	<1 (1/269)	3	2 (2/128)	4
Steroid utilization, % (n/N)	DLBCL: 10	27	10 (26/269) (CRS)	22-38	15[**]	22
Tocilizumab utilization, % (n/N)	DLBCL: 24 ALL: 48	43	18 (48/269) (CRS)	26-59	52[**]	69
Bridging therapy, %	DLBCL: 92	Not allowed in ZUMA-1 trial (used in real- world practice)	59	37	88	Allowed
Median CAR T cell dose	3.1×10^6 cells/kg	2×10^6 cells/kg	50, 100, 150 $\times 10^6$ cells/kg	2×10^6 cells/kg	150, 300, 450 $\times 10^6$ cells/kg	Target dose 0.75×10^6 cells/kg
LD chemotherapy	Flu 25 mg/m^2 × 3d + Cy 250 mg/m^2 × 3d or B 90 mg/m^2 × 2 d	Flu 30 mg/m^2 × 3 d + Cy 500 mg/m^2 × 3 d	Flu 30 mg/m^2 × 3 d + Cy 300 mg/m^2 × 3 d	Flu 30 mg/m^2 × 3 d + Cy 500 mg/m^2 × 3 d	Flu 30 mg/m^2 × 3 d + Cy 300 mg/m^2 × 3 d	Flu 30 mg/m^2 × 3 d Cy 300 mg/m^2 × 3 d

MCL indicates mantle cell lymphoma; PMBCL, primary mediastinal B cell lymphoma; CR, complete response; sCR, stringent CR; PFS, progression-free survival; NR, not reported; ICANS, immune effector cell-associated neurotoxicity syndrome; FL, follicular lymphoma; PBMC, peripheral blood mononuclear cells; B, bendamustine.

* As of this writing, the US FDA has granted priority review to the biologics license application for cilta-cel.

† A CAR-T construct with 2 BCMA-targeting single-domain antibodies.

‡ Per Penn criteria.

§ Per Lee et al. criteria [74].||Per American Society of Transplantation and Cellular Therapy (ASTCT) criteria.

¶ ICANS per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

\# CRS was graded by Lee et al. [74] and ICANS by CTCAE v5.0 (in phase 1b). CRS and ICANS were graded by ASTCT criteria (in phase 2). Lee et al. [74] and CTCAE v5.0 were mapped to ASTCT for CRS and ICANS, respectively.

** Given for CRS. Corticosteroid and tocilizumab utilization increased with increasing CAR T cell dose.

least 25 months after CAR-T infusion despite the absence of CD19$^+$ and CD20$^+$ B-cells [54]. Similarly, another study showed a preserved antiviral humoral immune response and a low incidence of viral infections after 90 days in 39 CAR-T recipients [86].

Prolonged Cytopenia and Risk of Infection

Prolonged cytopenia is a common complication in CAR-T recipients and limits further treatment options, including accrual into clinical trials. Hematologic toxicities, particularly beyond 30 days after CAR-T infusion, remain unexplored. A single-center study of 76 patients with R/R ALL enrolled in phase 1/2 clinical trials of CAR-T targeting CD19, CD22, and CD19/22 showed that 70% of patients developed new-onset severe neutropenia ($<0.5 \times 10^9$/L), 53% developed severe anemia (<60 g/L), and 48% developed severe thrombocytopenia ($<20 \times 10^9$/L) [87]. The severity of CRS was independently correlated with neutrophil recovery. In another single-center study, most of the 35 evaluable patients with ALL and lymphoma (14 pediatric and 21 adults) enrolled in a phase 1b/2 study developed hematologic toxicities following CD19$^+$ CAR-T infusion [88]. Twenty-eight responding patients (97%) developed neutropenia ($<1.5 \times 10^9$/L), 21 (72%) developed severe neutropenia ($<0.5 \times 10^9$/L), and 8 (28%) developed severe thrombocytopenia ($<50 \times 10^9$/L). There was a non-statistically significant correlation between severe hematologic toxicity and grade $\geq$2 CRS [88]. Similarly, another single-center study including 125 patients who received CD19$^+$ CAR-T for various clinical indications identified CRS grade as independently associated with impaired hematopoietic recovery after CD19$^+$ CAR-T therapy [89].

More recently, a large multicenter analysis examined predictive biomarkers of hematologic toxicity and aimed to develop a predictive model (CAR-HEMATOTOX) to allow risk-adapted management [90]. The analysis included 258 patients receiving axi-cel or tisa-cel for R/R LBCL and showed profound ($<0.1 \times 10^9$/L) and prolonged ($\geq$21 days) neutropenia in 72% and 64% of patients, respectively. The incidence and severity of CRS and ICANS and peak cytokine levels were not associated with the primary endpoint of the duration of severe neutropenia until day+60. The model included markers associated with hematopoietic reserve (eg, platelet count, hemoglobin, absolute neutrophil count) and baseline inflammation (eg, C-reactive protein, ferritin). A high score was associated with a longer duration of neutropenia (12 days versus 5.5 days; $P < .001$) and higher incidences of severe thrombocytopenia (87% versus 34%; $P < .001$) and anemia (96% versus 40%; $P < .001$) [90].

Potential for G-CSF in Preventing Infections in the CAR-T Setting

CRS development is directly related to *in vivo* T-cell expansion and massive production of T-cell effector cytokines, including IL-6, IFN-γ, and GM-CSF. Preclinical data have shown that IL-6, a key cytokine in CRS development, is produced predominantly by monocytes and macrophages [91–93]. However, clinical data on the utilization of G-CSF in CAR-T therapy are limited and conflicting. G-CSF drives myeloid precursor proliferation and differentiation and functionally activates phagocytosis through induction of the IgG receptor FcγRI [94]. Recombinant G-CSF is used to hasten neutrophil recovery and prevent infections after alloHCT [95]. However, in the CAR-T setting, myeloid growth factors can potentially increase the incidence and/or severity of CRS and ICANS via induction of proinflammatory cytokine secretion from monocytes and macrophages [76,77].

To that end, a small single-center study examined the impact of G-CSF in axi-cel recipients with R/R DLBCL. Seven patients (31.8%) received G-CSF at the physician's discretion. Although the median duration of neutropenia after LD chemotherapy was significantly shorter in the patients who received G-CSF (filgrastim) compared with those who did not (5 days versus 15 days; $P = .016$), there were no differences in the incidence and severity of infection based on G-CSF use. Interestingly, although there was no significant difference in the incidence of CRS or ICANS between the 2 groups, CRS severity was significantly greater in the patients who received filgrastim ($P = .042$) [96].

In another single-center study examining 70 recipients of axi-cel and tisa-cel with R/R DLBCL, 42 (60%) received prophylactic G-CSF and the other 28 (40%) did not receive G-CSF [97]. Although there was no difference between the 2 groups in terms of duration of neutropenia and infections, the patients in the G-CSF group were older (63 years versus 50 years; $P = .002$) and had a lower neutrophil count at day+0 as well as at day+5. Most patients in the study experienced grade 1-2 CRS, and there was no difference between the 2 groups in terms of incidence and severity of CRS. Similarly, 30% of the patients experienced ICANS, with no significant difference between the 2 groups [97].

Overall, the role of recombinant G-CSF in aiding neutrophil recovery in the CAR-T setting remains unexplored. Prospective studies are needed to examine the potential of G-CSF in preventing infectious complications after CAR-T versus the risk of greater on-target-off-tumor toxicities.

BCMA-Directed CAR-T and Risk of Infection

The pivotal phase-II KarMMa trial examined the safety and efficacy of ide-cel (bb2121; Abecma), a 4-1BB-based CAR-T construct directed against BCMA in patients with R/R MM previously treated with at least 3 prior lines of treatment [8]. The toxicity and safety endpoints are shown in Table 2. In terms of infectious complications, within 8 weeks of CAR-T infusion, 25% of the patients developed an infection due to an unspecified pathogen, 16% had a bacterial infection, 15% had a viral infection, and 7% had a fungal infection. The frequency of infections was increased between 8 weeks and 6 months after CAR-T infusion, with 40% of the infections due to an unspecified pathogen, 21% viral, and 3% each bacterial and fungal infections.

The FDA has also granted priority review to the biologic license application for another CAR-T product for treating patients with R/R MM who had received $\geq$3 prior regimens. Ciltacabtagene autoleucel (cilta-cel) has 2 BCMA-targeting single-domain antibodies and was examined in the phase 1b/2 CARTITUDE-1 study (ClincialTrials.gov identifier NCT03548207). Ninety-five percent of the patients developed CRS, including 4% with grade 3/4 CRS. Fifty-eight percent of the patients developed infections, including 20% with severe infections (grade $\geq$3) and 4% with sepsis (Table 2) [98].

Risk for Infections with Target Tumor Antigen CD19 versus BCMA

The evolving data described above suggest that CAR-T targeting CD19 likely results in more bacterial infections, whereas viral infections could theoretically occur more commonly following BCMA-directed CAR-T, along with a generally increased risk for overall infections and diminished vaccine responses. This selective predilection for viral infections in a BCMA-directed CAR-T construct possibly stems from the indigenous immunologic properties of the antigen and cell surface

expression. BCMA is selectively expressed on malignant PCs, normal PCs, and some mature B-cells and has an active role in the differentiation of B-cells into PCs [31,99-101]. The preferential susceptibility to viral infections in the setting of BCMA-directed CAR-T immunotherapy was illustrated in a patient who initially had a decline in plasma SARS-CoV-2 virus with antiviral treatment but ultimately succumbed to recurrent viremia at 71 days following the initial diagnosis [21].

The differential risk of infections has been demonstrated in a single-center retrospective analysis that examined infection outcomes up to 1 year after anti-BCMA- and -CD19-directed CAR-T therapy. Of the 104 patients included in the study, 55 (53%) had R/R MM and received BCMA$^+$ CAR-T, with a median of 6 prior lines of therapy, and 49 had NHL (47%) and received CD19$^+$ CAR-T, with a median of 3 prior lines of therapy. Almost all patients were receiving antimicrobial prophylaxis at the time of CAR-T infusion and did not exhibit severe lymphopenia, neutropenia, or hypogammaglobulinemia prior to LD. There were significant differences in the incidence of viral and bacterial infections between the recipients of BCMA CAR-T and recipients of CD19 CAR-T. The BCMA cohort had 19 bacterial infections (40%), compared with 29 bacterial infections (73%) in the CD19 cohort (P = .005), and had 25 viral infections (53%) compared with 8 viral infections (20%) in the CD19 cohort (P = .002). Fungal infection rates were comparable in the BCMA and CD19 cohorts (3 [6%] versus 3 [8%]; P = 1). The BCMA cohort had a higher rate of respiratory infections (68% versus 50%; P = .1), whereas the CD19 cohort had higher rates of bloodstream infections (15% vs 2%; P = .05) and gastrointestinal infections (10% versus 0%; P = .04). Again, corticosteroid use (incidence rate ratio, 1.6; 95% confidence interval, 1.1 to 2.5; P = .03) and post-CAR-T hypogammaglobulinemia (IgG <600) (incidence rate ratio, 2.1; 95% confidence interval, 1.2 to 3.9; P = .02) were associated with increased of infections, after adjustment for time periods [102].

Risk of Infections with Underlying Diseases and Treatment

In addition to the TAA, the underlying disease for which CAR-T therapy is indicated further determines the infection risk. The conditioning regimen and intensity, prior treatment regimens, prior receipt of cellular and immunotherapy, the interval between last treatment and CAR-T, as well as disease status at the time of CAR-T also contribute to the cumulative risk of infection after CAR-T. For instance, the duration and depth of neutropenia determine overall infection risk in patients receiving multiagent cytotoxic chemotherapy, such as in acute leukemia and lymphoma. Further, natural killer cell- and T-cell-mediated cytotoxicity is impaired with patients with ALL and is worse in patients with T-ALL compared with those with B-ALL [103]. Patients with chronic lymphoblastic leukemia (CLL) and MM have an inherent predisposition to infections associated with hypogammaglobulinemia and compromised humoral immunity [104–106]. Patients with MM are at especially higher risk of bacterial and viral infections due to a globally compromised immune system [107,108]. These patients may be at a particularly higher risk for severe COVID-19, as well as suboptimal vaccine responses.

The addition of monoclonal antibodies, immunomodulators, and small molecules to the backbone of frontline regimens further compounds the risk of distinctive infections. For instance, viral reactivation may occur following tyrosine kinase inhibitors, Janus kinase inhibitors, and monoclonal antibodies, and there is an increased risk of pneumonia due to *Pneumocystis jirovecii* with purine analogs, *in vivo* T cell-depleting agents, corticosteroids, and phosphatidylinositol 3-kinase inhibitors.

COMMON SARS-COV-2 VACCINE PLATFORMS

Vaccine development against SARS-CoV-2 has used several platforms, including inactivated, protein subunit, replication-incompetent viral vector-based, and nucleic acid-based platforms [109]. The nucleic acid vaccine platform has been most widely used to develop the SARS-CoV-2 vaccine due both to the rapidity of large-scale manufacturing and to early data demonstrating considerable efficacy. Nucleic acid vaccines mimic natural infection with endogenous antigen production and elicit strong T- and B-cell responses while being noninfectious. The mRNA vaccines are preferred over DNA and other vaccine platforms as mRNA is transient, avoids antivector immunity, and is delivered to the cytosol, preventing the risk of host genome integration [110].

Both mRNA vaccines used in the United States—BNT162b2, developed by Pfizer and BioNTech, and mRNA-1273, developed by Moderna—are lipid nanoparticle-formulated nucleoside-modified mRNA vaccines. The vaccines encode the SARS-CoV-2 full-length spike protein and are given either as a 2-dose regimen 21 days apart (for BNT162b2) or 28 days apart (for mRNA-1273) [111–113].

Both mRNA vaccines provide adequate protection against symptomatic COVID-19 that is mediated by a combined humoral and cellular immune response [48,114]. Clinical trials have demonstrated humoral immune response with antispike antibody titers remaining above convalescent controls after the second vaccine dose [115]. Cellular immune studies also have shown expansion of spike-specific CD8$^+$ and Th1 subtype CD4$^+$ T-cell responses, with a high fraction producing IFN-γ [49]. Longitudinal serologic studies and immune kinetics are awaited.

CURRENT RECOMMENDATIONS FOR SARS-COV-2 VACCINATION FOR CANCER PATIENTS

The efficacy and safety of SARS-CoV-2 vaccines have not been examined in immunocompromised patients, because these patients were excluded from clinical trials. Although all cancer patients should be considered "highly prioritized," the optimal dosing and timing for COVID-19 vaccination remain elusive in this population. Expert opinion of a committee of the Society for Immunotherapy of Cancer recommends that cancer patients receiving immunotherapy should receive SARS-CoV-2 vaccination [116]. The American Society of Clinical Oncology also recommends that all cancer patients receive SARS-CoV-2 vaccination unless otherwise contraindicated by the Centers for Disease Control. The American Society of Transplantation and Cellular Therapy, American Society of Hematology, and National Comprehensive Cancer Network currently recommend the administration of mRNA SARS-CoV-2 vaccines as early as 3 months following CAR-T [17,58,117,118]. Further recommendations related to vaccines in general in the pre- and post-CAR-T period are outlined elsewhere [58].

These guidelines are based on evidence demonstrating efficacy and safety in the general population and acknowledge that efficacy may be reduced among recipients of cellular therapy compared with the general population. This is further compounded by the novelty of the mRNA vaccine platform (with a dearth of longitudinal data) and lack of established anti-SARS-CoV-2 spike binding (anti-S IgG) and neutralizing antibody titers even in the general population. Furthermore, the level of humoral response that correlates with clinical protection remains unknown. A suboptimal response to the SARS-

CoV-2 vaccine has been demonstrated in patients with advanced hematologic malignancies [51]. Moreover, the durability of the immune response and the correlation between *in vitro* assays and overall vaccine efficacy in immunocompromised patients are yet to be determined.

CURRENT STATE OF SARS-COV-2 VACCINE RESPONSES IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Evolving data suggest that patients with hematologic malignancies may have a diminished immune response to the SARS-CoV-2 vaccine [119]. Underlying diseases, overall state of immunosuppression, remission status, receipt of active treatment, and immune reconstitution profile may impact the response (Table 1). Diminished vaccine responses have been described in patients with CLL and MM. B-cell depletion, active treatment with BTK inhibitors, and IgA deficiency have been associated with an inadequate humoral response [120–123]. In the largest study of patients with hematologic malignancies reported to date, comprising 1455 patients, seroprotective antibodies were analyzed 14 days after the second dose of mRNA vaccine, and the data showed superior immune responses to both mRNA vaccines in patients with leukemia, MM, and Hodgkin lymphoma compared with those with B-cell NHL subtypes [124]. These suboptimal response rates to mRNA-based vaccines in patients with hematologic malignancies are in congruence with those demonstrated previously with other nonlive vaccines against a variety of illnesses [125–127].

DATA ON VACCINE RESPONSE IN CAR-T RECIPIENTS AND ADDITIONAL IMMUNE CONSIDERATIONS

In addition to concerns related to suboptimal efficacy, CAR-T recipients theoretically could have an elevated risk of immune-mediated toxicity. Evidence in immunocompetent individuals have demonstrated robust release of cytokines, including IFN-γ, TNF, IL-1, IL-2, and IL-12, and hemophagocytic lymphohistiocytosis, in addition to the production of neutralizing antibodies and virus-specific $CD4^+$ and $CD8^+$ T-cells [48,128,129]. In addition, the incidence of cytopenia and immune-mediated thrombocytopenia, reported in healthy subjects, also needs to be explored prospectively in CAR-T recipients [130,131].

Data are now evolving related to the immune response to the SARS-CoV-2 vaccine. A prospective single-center study examined serologic and cellular immune responses in a cohort of alloHCT and CAR-T recipients who received BNT162b2 mRNA COVID-19 vaccine. Seroprotective antibodies were analyzed in 14 CAR-T recipients who had maintained remission after CAR-T infusion at 7 to 14 days after the second vaccine dose with an immunoassay that detected qualitative and semiquantitative IgG to SARS-CoV-2 spike protein receptor-binding domain (RBD). Antispike cellular response was evaluated using the ELISpot assay for the detection of peptide-induced IFN-γ and IL-2 secretion. Positive serology was detected in 5 patients (36%), and ELISpot was positive in 6 patients (50%). Three patients had complete B-cell aplasia, all 3 of whom were CAR-T recipients. As expected, B-cell reconstitution correlated with positive serology compared with those with B-cell aplasia (66% versus 11%; $P = .025$). In subgroup analyses, the ELISpot results correlated with the $CD4^+/CD8^+$ ratio, whereas the numbers of $CD19^+$, $CD4^+$, and $CD8^+$ cells did not significantly correlate with the probability of positive test results. Interestingly, a higher number of $CD19^+$ cells was associated with a positive humoral response to the vaccine in a multivariate analysis of the entire study cohort, in addition to female sex and a longer time from infusion of cells. Even though the study reported an overall *in vitro* response of 57% among CAR-T recipients, it is noteworthy that humoral immune response was observed only in 36% of the patients, and that only one-half of those patients had evidence of cellular response. Although there were no grade 3-4 nonhematologic adverse events, 4 patients in the entire cohort of alloHCT and CAR-T recipients (5%) developed grade 3 or 4 thrombocytopenia (n = 3) or neutropenia (n = 1) [132].

Another single-center retrospective study examined humoral immune response to SARS-CoV-2 vaccines (predominantly mRNA-based) in 130 patients, including 14 CAR-T recipients. The study used an enzyme immunoassay that correlated with neutralizing immunity and tested for antibodies against the S1 domain of the spike protein. Positive serology was detected in only 11% of the CAR-T recipients. The seropositivity rate was considerably diminished in patients who had received corticosteroids and those who had undergone CAR-T infusion within 6 months of vaccination [133].

In the largest study examining patients with hematologic malignancies reported to date comprising 1455 patients, seroprotective antibodies were analyzed in a small cohort (n = 12) of CAR-T recipients at 14 days after the second mRNA vaccine dose with an immunoassay that detected semiquantitative IgG to SARS-CoV-2 spike protein RBD [124]. The vaccine responses differed considerably in the CAR-T recipients and depended on the TAA and the underlying disease. Although only 1 of 7 $CD19^+$ CAR-T recipients had a positive antibody response to the vaccine, 4 of 5 patients with MM who had received $BCMA^+$ CAR-T or $CD138^+$ CAR-T exhibited a robust humoral response. Interestingly, the 1 $CD19^+$ CAR-T recipient who responded positively had relapsed CLL immediately before the mRNA vaccination. Also, the 1 $BCMA^+$ CAR-T recipient who responded negatively underwent immune analysis at 14 days after the second mRNA vaccine dose, and the negative result was likely due to insufficient time to generate an antibody response [124]. Considering that B-cell aplasia is a clinical surrogate marker of CAR-T persistence, the robust antibody response in patients with MM may forecast a lack of durability of $BCMA^+$ CAR-T. Longitudinal data related to CAR-T efficacy as well as vaccine responses in CAR-T recipients are awaited.

The foregoing analyses were heterogeneous and limited by low statistical power. Nonetheless, they indicate that humoral responses are substantially diminished in CAR-T recipients and may be driven by the underlying disease and immunocompromising potential of the treatment. These results must be interpreted with caution, given the limitations of small sample sizes, differences in immunoassays, and lack of standard definitions and clinical correlates of SARS-CoV-2 immune response.

IMMUNOSUPPRESSED MILIEU AS A DRIVER FOR MUTATIONAL SARS-COV-2 VARIANTS

Immunocompromised patients are at increased risk for shedding of the replication-incompetent virus [22,51]. Patients with hematologic malignancies undergoing active treatment, particularly B-cell-depleting therapy such as CAR-T, are at a higher risk for prolonged viral shedding. Prolonged use of corticosteroids has been shown to impact viral kinetics in a similar manner. The differential pattern of viral receptor expression and tropism in immunocompromised patients have been reviewed elsewhere [51,134]. Several recent reports have suggested that SARS-CoV-2 variants of concern, with greater transmissibility and pathogenicity, can arise during a protracted course of COVID-19 [135,136]. Multiple mutations

result in the generation of clinical and public health concern variants. These mutations predominate in the spike protein, which is the prime target of the protective antibody response and mediates viral entry.

POTENTIAL STRATEGIES TO BOOST VACCINE RESPONSE IN CAR-T RECIPIENTS

Additional vaccine doses are likely needed in patients with profoundly suppressed humoral immunity and a high cumulative risk of severe infection (Table 1). Early studies have demonstrated the feasibility of CARλ and CARκ T cells that do not lead to B-cell aplasia and thus have the potential for a minimal impact on humoral immunity [137]. Meanwhile, the timing and intensity of corticosteroid use for the prevention and treatment of CAR-T toxicities should be reviewed, given the potential for diminished immune responses [138]. Accumulating evidence related to the heterologous prime boost with alternate vaccine technologies also shows promise [139,140]. Initial studies have shown that sequential immunization with adenovirus vectored vaccine and inactivated, recombinant subunit, and mRNA vaccine administration results in higher levels of neutralizing antibodies, more potent humoral immune responses, and greater T-cell reactivity [141]. However, longitudinal studies are needed to determine the optimal sequence, vaccine platform, and timing to establish safety and reduce vaccine-associated reactogenicity in profoundly immunosuppressed CAR-T recipients. Evidence from the SARS-CoV-1 epidemic showed significantly greater durability with memory T-cell response compared with antibodies [47]. The results of prospective mechanistic studies, such as Center for International Blood and Marrow Transplant Research study SC21-07/BMT-CTN 2101, are awaited [46,142-145]. Furthermore, long-acting monoclonal antibodies or small molecules potentially resistant to current SARS-CoV-2 mutations will need evaluation in prospective studies of cellular therapy recipients. In addition, halting active viral replication with antiviral agents to prevent the development of mutations remains an unmet need.

FUTURE DIRECTIONS

Immunity to SARS-CoV-2 is conferred by intricate crosstalk of both antibody and T-cell responses. Insight into both responses is needed for an optimal understanding of protection in this vulnerable patient group. Longitudinal serologic and cellular studies are essential to understand the duration of immunity and to address whether revaccination or boosting is required and whether this is contingent on the TAA that the CAR T cells are designed to target. Telemedicine should be incorporated at the core of long-term follow-up to minimize the exposure of immunosuppressed patients to the hospitals and the community. Until the data become available, the risk of nosocomial transmission should be minimized by vaccinating all healthcare workers caring for patients with hematologic malignancies, and strict mitigation strategies should remain in place at all cancer centers.

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