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Infectious Complications of Chimeric Antigen Receptor (CAR) T-Cell Therapies

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Abstract

CAR T Cells have revolutionized the treatment of many hematological malignancies. Thousands of patients with lymphoma, acute lymphoblastic leukemia and multiple myeloma have received this “living medicine” and achieved durable remissions. Their place in therapy continues to evolve, and there is ongoing development of new generation CAR constructs, CAR T Cells against solid tumors and CAR T Cells against chronic infections like human immunodeficiency virus and hepatitis B.

A significant fraction of CAR T Cell recipients, unfortunately, develop infections. This is in part due to factors intrinsic to the patient, but also to the treatment, which requires lymphodepletion (LD), causes neutropenia and hypogammaglobulinemia and necessarily increases the state of immunosuppression of the patient. The goal of this review is to present the infectious complications of CAR T Cell therapy, explain their temporal course and risk factors and provide recommendations for their prevention, diagnosis, and management.

Keywords

chimeric antigen receptor (CAR); cytokine release syndrome; opportunistic infection; neutropenia; hypogammaglobulinemia

Infections following CAR T Cell therapy: Frequency and Risk Factors

The main toxicities of CAR T cell therapy are cytokine release syndrome (CRS), the neurological syndrome called Immune Effector Cell (IEC) Associated Neurologic Syndrome (ICANS), and cytopenias.[1-3] Hypogammaglobulinemia is an expected consequence of CAR T cells directed against B cells and may last years.[4] In addition, and partly related to those side effects, infection is a common complication of CAR T therapy, and a cause of significant morbidity and mortality.[5]

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The FDA-approved CAR T-cell constructs result in any infection in 45% to 72% of patients, and severe infection in 12 to 48%, with differences between the different CAR constructs and, with the same construct, between different indications. Post-marketing studies of two Anti-CD19 CAR T in adults (tisagenlecleucel and axicabtagene ciloleucel) suggest increased infectious risk with tisagenlecleucel [6,7], although this type of analysis is prone to bias. The patient's baseline risk and state of immunosuppression seems extremely important in terms of infectious risk, since infections appear to be more common in patients with relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL) than in patients with diffuse large B cell lymphoma (DLBCL) or follicular lymphoma (FL) treated with the same CAR T (tisagenlecleuce).[8-10]

According to FDA documentation, the frequency of all infections/severe infections of the approved anti-CD19 CAR T-cell products was as follows: tisagenlecleucel: 72%/48% of r/r ALL [8], 58%/33% of r/r DLBCL [9] , 52%/21% of FL [10] ; axicabtagene ciloleucel (axi-cel): 45%/17% of patients with non-Hodgkin lymphoma (NHL) [11]; brexucabtagene autoleucel: 56%/30% of mantle cell lymphoma (MCL) [12] and 44%/30% of ALL [13]; lisocabtagene maraleucel: 36% and 12% in r/r large B cell lymphoma[14]. The frequency of infections/severe infections with the anti-B-cell maturation antigen (BCMA) CAR T-cell were 70%/23% for idecabtagene vicleucel [15] and 59%/23% for ciltacabtagene autoleucel [16]. Not surprisingly, infections increase the risk of death [17].

A systematic review and meta-analysis to determine the frequency of severe infection in patients with hematological malignancies receiving CAR T-cell therapy included 45 studies (including 34 randomized controlled trials (RCT)) with 3591 patients [18] and found the overall frequency of infection of 33.8% and of severe infection 16.2%.

The frequency and type of infection varies over time, with most infections (particularly severe infections) occurring in the first few weeks after infusion. This is probably because different predisposing factors occur at different points in time.

The infection risk in the setting of cellular therapies is contingent on host-specific factors and factors related to the treatment. Eligible patients may be very immunocompromised at baseline, with relapsed or refractory leukemia, lymphoma, or multiple myeloma (MM) status post multiple lines of treatment including hematopoietic stem cell transplant (HCT). Frequently some extra chemotherapy or high-dose corticosteroids are given to control the cancer during the 3-4 weeks needed for the generation of the CAR T cells (bridging chemotherapy). In addition, lymphodepleting therapy (typically fludarabine + cyclophosphamide) is usually given before infusion of the cells, and results in near-universal early neutropenia and prolonged lymphopenia. Naturally, anti-CD19 CAR T cells will cause B cell depletion and possibly hypoglobulinemia. The dose of CAR T cells has been associated with infection risk in some studies. Different CAR constructs may result in different patterns of immune response and, consequently, different risks of CRS or ICANS and possibly immune dysregulation that could conceivably facilitate infection. In the presence of clinically significant CRS or ICANS, immunomodulatory/immunosuppressive therapy is initiated, typically tocilizumab and corticosteroids, and these may facilitate infection.

Potential contributors to late infection include persistent neutropenia (a significant proportion of CAR T recipients experience neutropenia beyond the fourth week after infusion) [19-21], persistent hypogammaglobulinemia [4](since B cells are the target of Anti-CD19 CAR T-cells and plasma cells the target of anti-BCMA CAR T-cells) and delayed immune reconstitution[22,23].

The purpose of this narrative review is to familiarize the reader with the infections (common and uncommon) that have been associated with cellular immunotherapy, their clinical presentation, their risk factors, and the currently recommended strategies to prevent and manage them.

Early Infections Associated with CAR T-cell Therapy

A number of studies focus on (or distinguish) infections during the first 28 or 30 days following CARTs, as opposed to infections that occur later. Neutropenia and CRS and its treatment take place during this period. Some of these publications present single-institution experience combining different phase I-II clinical trials of experimental CAR T cell constructs [24-28], but other address infections following the commercially available products.[22,29,30].

Hill et al described the experience at the Fred Hutchinson Cancer Research Center with CD19 targeted CARTs in 133 adult patients (47 with acute lymphoblastic leukemia (ALL), 24 with chronic lymphocytic leukemia (CLL) and 62 with non-Hodgkin lymphoma (NHL). [24] All patients received lymphodepletion chemotherapy, and antimicrobial prophylaxis with acyclovir or valacyclovir and trimethoprim sulfamethoxazole for 3 months and levofloxacin and fluconazole during neutropenia. Immunoglobulin G (IgG) was monitored and IVIG was recommended for IgG < 400 mg/dL.

During the first 28 days after CART infusion there were 43 infections in 30 of the 133 patients (23% of patients developed infection), resulting in an infection density of 1.19 infections per 100 days at risk. There were 24 bacterial infections (12 bacteremia), 13 viral infections (10 respiratory viruses, 1 case of Epstein-Barr Virus (EBV) and 1 case of Cytomegalovirus (CMV) viremia, both without end-organ disease) and 6 invasive fungal infections (IFI) in 4 patients, including two with mold infections. Of note, all the patients with IFI had severe CRS or ICANS requiring tocilizumab and/or corticosteroids. In the 28 patients who developed CRS and infection, infection preceded CRS in only three cases. The median times to the onset of CRS and infection were 1.9 and 6 days, respectively.

The experience with pediatric/young adult patients at the University of Washington was subsequently published by Vora et al, who used very similar definitions and methods as Hill and colleagues.[26] Eighty-three patients (median age 12), almost all with refractory or relapsed ALL, were included in this study. Fifty-five percent had received an allogeneic hematopoietic stem cell transplant (HCT). Interestingly, 54% of the patients had an infectious episode in the 90 days before CART infusion, demonstrating the high risk of the cohort. In the first 28 days after CART infusion 33 patients (40%) experienced 37 infections (20 bacterial, including 16 episodes of bacteremia, sixteen viral (mainly respiratory viruses),

including two patients who developed herpes zoster (not on prophylactic acyclovir) and one fungal (mucormycosis with *Cunninghamella* while on voriconazole, unclear whether this was worsening of prior infection or new infection). The calculated infection density was 2.89 infections per 100 days at risk during the first 28 days (more than twice the one found in adults [24].

Park et al described their experience with 53 patients with relapsed ALL receiving anti CD19 CAR T cells at Memorial Sloan Kettering Cancer Center.[27] There were 26 infections (17 bacterial, 5 viral, 4 fungal) in 22 patients during the first 30 days (42% of patients experienced early infection). In this homogeneous cohort, severe CRS (grade 3 or higher) was associated with risk of subsequent infection (between day 31 and 100), and there were 3 infection-related deaths.

The experience at the National Institutes of Health (NIH) Clinical Center in 162 adult and pediatric patients enrolled in phase I clinical trials with CAR T cells directed against a variety of antigens (CD19, CD22, disialo-ganglioside (GD2) or B-cell maturation antigen (BCMA)) was reported by Mikkilineni and her colleagues [25]. Most patients were included in pediatric/young adult research protocols, and the median age for the whole cohort was 19 years (range 4-69).

They documented 76 infections in 53 of the 162 patients (33% of patients had infection) and they also found bacterial infections (mainly bacteremia) were most common, viral infections were almost as common, and fungal infections were rare (only 2 “possible” fungal infections). Of the viral infections, respiratory viruses predominated (14 upper respiratory infections) but there were also cases of herpes simplex (n=2, one of them on prophylaxis), herpes zoster (n=1, on prophylaxis) and CMV (2 cases of viremia and, notably, one case of CMV pneumonitis). Salient points of this paper include that almost 20% of infections took place between lymphodepletion and CART infusion; high frequency of *Clostridiodes difficile* (*C. difficile*) infection (seventeen cases (10%), although, given the fact the diagnosis was made just by polymerase chain reaction (PCR) testing, the investigators acknowledge that some patients may have just been colonized and develop diarrhea with the lymphodepleting chemotherapy). Other findings were 1) there were many more infections in the subgroup receiving anti-CD22 CART (compared to anti-CD19) and 2) the patient’s individual history (type of malignancy, prior treatments, prior infections) was important: infections were most common in MM patients receiving anti-BCMA CAR T and, in multivariate analysis, increased prior lines of chemotherapy and having had at least 1 infection within 100 days of LD were associated with increased risk of infection.

Israeli investigators have published their experience with anti-CD19 CAR T cells in 88 patients with r/r leukemia and lymphoma. Similar to other groups, they found 36 infections in 24 patients during the first month post-infusion, 22 bacterial infections (six bacteremia episodes) and 14 viral, including 2 cases of CMV (viremia and pneumonitis)l [31], for an infectious density of 1.28 infections per 100 days at risk

A single-institution report from China addressed early infections in 109 patients following experimental CAR T-cell therapy with anti-CD19/anti-CD22 (in r/r B-cell malignancies

and post-autologous HCT) and anti-BCMA CAR in r/r plasma cell malignancies.[32] They registered only 19 infections (14 bacterial, 3 viral, 2 fungal) in 19 patients during the first 30 days. Most infections happened after CRS onset and more severe infections took place during neutropenia. Five patients died of infection. A subsequent study from the same institution, available only in Chinese, reports 170 patients with hematological malignancies (ALL n=72, NHL n=56, MM n=42) also identified bacterial infections as most common (98 infections in 78 patients), followed by viral (14 infections in 14 patients) and fungal (7 infections in 7 patients).[28] All the fungal infections happened in patients with severe CRS who received tocilizumab and/or corticosteroids.

The papers discussed so far used experimental CAR T cell constructs and often combined different research protocols. In contrast, three single-institution retrospective studies have described the infections following the use of the FDA-approved axicabtagene ciloleucel (axi-cel) [22,29] or axi-cel and isagenlecleucel [30]. These three papers provide one year of follow-up and confirm some of the observation of the earlier studies: more infections and more severe infections developed in the first 30 days. The numbers were: 31 of 85 patients (36%) (including 11 severe infections with three deaths) in the study from Moffitt Cancer Center [29]; 37 infections in 60 patients (62%) (including 19 severe infections) in the study from Memorial Sloan Kettering Cancer Center [30] and 19 infections (6 severe) in 41 patients (46%) from Stanford, for an infection density of 2.35 infections per 100 days at risk.[22]. The Stanford cohort differs in that these patients had more viral (mostly respiratory) than bacterial infections, although most severe infections were bacterial.

There are fewer publications focusing on infections following anti-BCMA CAR T cells [33-35]. Overall, viral infections have been documented more frequently than bacterial following anti-BCMA CAR T cells, but bacterial infections still predominated during the first 8 weeks in the pivotal study of decabtagene vicleucel [15]. Kambhampati and colleagues reported their experience with adult patients with MM who were treated with BCMA CAR-T at the University of California, San Francisco (UCSF) between 2018 and 2021 [35]. During a median follow-up of six months, 29 of the 55 patients (53%) suffered 47 infectious episodes (25 viral (all respiratory viruses), 19 bacterial (4 bacteremia), 3 fungal (2 aspergillosis, one of them fatal)). Half the infections took place in the first 100 days. Most infections categorized as “severe” were bacterial. Mohan and colleagues [34] describe 26 patients who received anti-BCMA CAR T Cells with only five infections after a median follow-up of 9 months, with most infections taking place in the first 30 days.

A different look at the frequency and consequences of infection is provided by a multinational observational study of 241 patients who required ICU admission within 30 days of CAR-T cell infusion (typically for CRS, ICANS or both)[36]. Most patients received antibiotics, although infections were documented in a minority. The investigators found that 30 patients (12%) developed microbiologically documented bacterial infection, and they had significantly worse outcomes than the patients with “clinically documented infection” or “no infection”. Thirty-nine patients (19%) acquired infections in the ICU, including 11 fungal infections and 2 cases of invasive CMV.

As mentioned earlier, potential risk factors for infection during the first month include host-specific risk factors (e.g., specific malignancy, prior treatments, history of transplant), bridging chemotherapy, pre-infusion lymphodepleting chemotherapy, neutropenia and, potentially, CRS and its treatment. The studies discussed above (all retrospective) have studied all those risk factors, and there is only marginal consistency on the findings. This may be in part due to the nature of the data, the retrospective design and the different patient groups and different prophylaxis: the phase I-II studies mix patients on different protocols and with different CAR T constructs, and participants in these early-phase trials may be at higher risk of infection to begin with. The studies with the FDA-approved CAR T may be more homogeneous, but they include a small number of patients and use different methodologies and definitions. Systemic corticosteroid use was found to be a risk factor for infection in all three series [22,29,30] and remained significant by multivariate analysis in the Memorial and Stanford series [22,30]. Bridging therapy, severe CRS or ICANS grade and use of tocilizumab were significant only in univariate analysis in one of the three [29]. Although this may seem to contradict prior studies [27], it is worth mentioning that Park and colleagues found CRS grade 3 or higher was associated with subsequent infection risk: infections between day 31 and 180. Regarding tocilizumab, there is a retrospective registry study that analyzed 1397 adult patients who received CAR T cells between 2016 and 2019, 882 of whom developed CRS. In the 394 patients with Grade 1 CRS there was no difference in infection rate between those who received tocilizumab (typically a single 8 mg/kg dose) and those who did not.[37] Given the limitations of registry studies in general and the relatively narrow group analyzed, it is not clear whether the question is settled. Tocilizumab is associated with increased bacterial infections when it is used chronically in rheumatoid arthritis [38] and with both bacterial and fungal infections when used in COVID-19 patients [39,40].

In summary, the risk of severe bacterial infection is highest early after CAR T cell infusion. Most severe bacterial infections are bacteremia or pneumonia. *C. difficile* is frequently found in the stool, but the possibility of ascertainment bias complicates the interpretation of this finding. The timing of bacterial infection overlaps with neutropenia and CRS, but it typically follows the onset of CRS. Fever in the first few days post infusion is more commonly a manifestation of CRS, but infection should be considered and, if the patient is neutropenic, immediate initiation of empirical antibiotics for neutropenic fever is recommended.[41] It has been suggested that a “double peak” of interleukin 6 (IL-6) is helpful to identify patients with life-threatening infection [32], but this finding awaits corroboration. Admission to the ICU for CRS or ICANS seem to increase the risk of developing infection.[36]

Although most early viral infections are caused by respiratory viruses and categorized as mild, CMV infection, CMV pneumonia [25] and Human Herpesvirus 6 HHV-6 encephalitis [22] have been rarely seen. Early fungal infections are uncommon, and yeasts are more frequent than molds.

Infections after day +28

After day +28 viral infections (particularly respiratory viruses) predominate. The two studies from Seattle discussed earlier measured infections similarly and showed decreased infection density between day 28 and 90. In children, adolescents and young adults the infection density between day 28 and day 90 was 0.55 infections per 100 days-at-risk (7 respiratory viral infections, 5 bacterial infections and no fungal infections in 48 patients) [26]. In adults the infection density was 0.67 infections for every 100 days-at-risk, significantly less than in the first 28 days [24], including 13 viral infections in 11 patients, 8 bacterial infections in 7 patients and 2 fungal infections in 2 patients who had previously received allo-HCT. Similar infection density (0.6 per 100 days-at-risk) was found in Israel between days 31 and 60: 9 infections in 7 out of sixty-nine patients [31].

The studies on FDA-approved CAR T cells analyze immune reconstitution over one year and try to correlate infections with immunologic parameters [22,29,30]. In the Moffitt cohort, 32 infections were identified in 31 of 70 patients (44% of patients) after day 30, most of them (19) upper respiratory tract infections (URTI). Of the 12 bacterial infections, 7 were considered severe. No fungal infections were seen.[29] The investigators from Memorial document infections after day 30 in three time periods (Days 31-100, days 101-180 and after day 180) [30] and show that the frequency of respiratory viral infections remains relatively stable but bacteremia declines over time, with “localized infection without bacteremia” becoming the most common form of bacterial infection after day 30. In all, they had 35 bacterial infections in 16 patients, 28 viral (21 respiratory viruses, one CMV viremia, one BK cystitis and 2 cases of herpes zoster on prophylaxis). They had one case of *Pneumocystis jirovecii* pneumonia (PJP) (not on prophylaxis) 9 months after CAR T cell infusion. The cohort from Stanford also showed declining rates of severe infections over time, although they had three late cases of PJP (2 between day 29 and 180 and one after the one-year mark) [22]

Viral infections in a cohort of 61 patients with r/r MM patients treated with experimental anti-BCMA CAR T cells have been reported by Wang and colleagues.[33] Fifteen patients (25%) experienced 18 episodes of viral infection/reactivation after infusion: 4 EBV, 6 CMV, 3 Hepatitis B Virus (HBV) reactivation, 4 herpes zoster, and one COVID-19 (no other respiratory viruses were reported). The EBV reactivation episodes were asymptomatic and resolved without intervention. All the CMV episodes of reactivation happened after day 30 and followed treatment with corticosteroids. Three of the six episodes were associated with symptoms (although no biopsy-proven CMV disease is documented). All were treated. Two of the episodes of HBV reactivation happened despite prophylaxis with entecavir; the third one had anti-HBc antibody as the only marker of past hepatitis B and was not on entecavir prophylaxis. The zoster cases were not on any prophylaxis. The investigators conclude that viral reactivation of latent virus may be more common following anti-BCMA CAR T cells and recommend acyclovir and entecavir prophylaxis for patients at risk and CMV monitoring.

Potential contributors to infection risk after the first month include neutropenia, hypogammaglobulinemia, and delayed immune reconstitution. Whereas early neutropenia

is nearly universal, and generally attributed to the effect of lymphodepleting chemotherapy, neutropenia persisting beyond day 28 post CAR T Cell infusion is fairly common and it may be related to the CAR construct and the severity of CRS or ICANS [20,21]. Hypogammaglobulinemia may occur early (35% of adults show hypogammaglobulinemia between days 15 and 30 after anti-CD19 CAR T Cell infusion) and persist for a long time: 67% of adults at 90 days or later [4]. The association between hypogammaglobulinemia and infections has been shown in children, where replacement immunoglobulin was associated with a lower rate of sinopulmonary infections [42]. No clear association has been established in adults. A study of 65 recipients of anti-CD19 or anti-BCMA CAR T cells showed high prevalence of hypogammaglobulinemia in 30 adults (90%) but relatively preserved levels of antibodies against vaccine-preventable infections [23]

T cell recovery may take months following the lymphodepleting chemotherapy. In the Stanford cohort, 54.5% and 60% of patients had a CD4+ T-cell count < 200 cells at 6 months and one year, respectively. [22] This finding suggests that CAR T cell recipients may remain at risk for opportunistic infection for a long time. In fact, the three-year update of the ELIANA trial of tisagenlecleucel in patients with r/r ALL [43] found that infections were still frequent > 1 year after infusion, but the rate of grade 3 or 4 infection did not increase after one year .

Specific Infections

Bacterial Infections

Most severe infections are caused by bacteria. These infections occur early and seem related to the neutropenia and CRS and its treatment. *Clostridioides difficile* (*C. difficile*) infection is frequently reported, but part of this may be ascertainment bias since diarrhea may be part of CRS and elicit more frequent testing. In addition, depending on the test used, it may not be possible to differentiate colonization from true *C. difficile* disease.

Bacteremia and respiratory tract infection are the other commonly encountered bacterial infections. Multidrug resistant bacteria may be overrepresented in a population of heavily treated cancer patients.

The recently developed CAR-HEMATOTOX (HT) score performed well in a multicenter retrospective analysis to identify patients with severe bacterial infections [44]. Prospective studies are needed, but the score is easy to calculate (ideally on the day of lymphodepletion) with readily available laboratory data (absolute neutrophil count (ANC), hemoglobin, platelet count, CRP, and ferritin).

Viral Infections

Respiratory viruses are the most common viral infections. Most cases involve the upper respiratory tract only, but lower respiratory tract infections do occur and at least one death caused by influenza has been documented. [30]

EBV reactivation is uncommon and, apparently, inconsequential.

CMV reactivation is not seen commonly enough to recommend monitoring outside of the circumstances where it would be otherwise indicated (e.g., post-allo-HCT). That said, lethal CMV pneumonitis has been reported [25].

There have been at least two well-documented cases of HHV-6 in patients with lymphoma after receiving axicabtagene ciloleucel [22,45]

The significance of late cases of JC virus at 7 and 14 months post CAR T Cell infusion [46,47] is hard to ascertain, given the fact that PML may occur in patients with hematological malignancies on a variety of treatments.

HBV reactivation is a serious concern in all patients receiving anti-B cell therapy. Although many examples of successful use of CAR T-cells in patients with hepatitis B have been published, emphasizing cellular therapy is safe when using entecavir or tenofovir prophylaxis [48-51], there are also case reports of HBV reactivation with fulminant hepatitis without antiviral prophylaxis [52,53], and HBV reactivation despite entecavir use [33] CAR T cells have also been used safely and successfully in patients infected with HIV and hepatitis C virus [50]. Coronavirus disease 2019 (COVID-19) has worse outcomes in patients with hematologic malignancies [54]. This finding extends to patients who have received CAR T, with attributable mortality of 41% in a study from the European Society for Blood and Marrow Transplantation (EBMT) Infectious Diseases Working Party and the European Hematology Association (EHA) Lymphoma Group from early 2021 [55]. A survey from 18 European centers of CAR T-Cell recipients with symptomatic COVID-19 (January 2020-February 2021) reported overall mortality of 50% [56]. Recipients of Anti-CD19 CAR T Cells have weaker humoral response to COVID vaccines [57], but they seem to have normal (or even increased) cellular responses [58]

Fungal Infections

Fungal infections seem relatively uncommon. Yeast infections occur early, PJP occurs late and mold infections happen rarely, typically associated with classic risk factors like prolonged neutropenia and corticosteroids [59]. A recent single-center retrospective study of 280 adults who received anti-CD19 CAR T Cells identified 8 patients with fungal infection (2 yeasts, 3 mold and 3 PCP) [60], despite not using any prophylaxis against yeasts or molds. The three cases of PJP occurred at day 115, 390 and 441. Anti-Pneumocystis prophylaxis was used until day 180, but one patient was not taking the atovaquone that had been prescribed.

Parasitic Infections

There have been at least three reports of toxoplasmosis: one following DLBCL relapsed after autologous HCT [61], one after CAR T cells for relapsed ALL post allo-HCT [62] and another in relapsed DLBL treated with axicabtagene ciloleucel who received intense immunosuppressive treatment for severe CRS [63]. One case of cryptosporidiosis in the first 30 days with no details [30] and a case of Refractory cryptosporidiosis in an 85-year-old patient with lymphoma [64]

Prevention of Infection: Guidelines and Expert Recommendations

The European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA) have published “best practice” recommendations in 2020 [65] and 2022 [41]. The Spanish Infection Prevention in CAR T-cells Study Group [66] and the French Society of Bone Marrow Transplant and Cellular Therapy (Société Francophone de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC) [67] also published their own recommendations. In addition, several expert reviews are available [68-71].

Neutropenia: G-CSF should be avoided in the presence of CRS or ICANS (some data suggest G-CSF may increase their severity [72], but this is not a universal finding [73,74]). G-CSF may be started after day +14 or after resolution of CRS or ICANS. It may be considered early (day +5) if the patient is at risk of infection and should be considered if neutropenia persists beyond day +28

Antibacterial prophylaxis is not routinely recommended, but may be considered in prolonged neutropenia and following local guidelines

Anti-HSV and VZV prophylaxis with acyclovir or valacyclovir is recommended from LD until 1 year post-CAR T-cell infusion and CD4+ T cells > 200/μL

Anti-pneumocystis prophylaxis is recommended from LD until 1 year post-CAR T-cell infusion and CD4+ T cells > 200/μL

Systemic antifungal prophylaxis is not recommended routinely by the EBMT, but they suggest to consider posaconazole, fluconazole or micafungin in patients at higher risk [41] (e.g., history of fungal infection, severe or prolonged neutropenia, long-term corticosteroids or in patients post-allogeneic HCT). The Spanish group has a slightly more aggressive approach, including four or more prior treatment lines, high-dose of CAR T Cells and tocilizumab as risk factors to consider for anti-mold prophylaxis.[66] Some experts recommend broader use of mold-active antifungal prophylaxis until more data are available [69,75]

Intravenous Immunoglobulin should be used routinely in children and may be considered in adults with serious/recurrent infections and hypogammaglobulinemia (IgG < 400 mg/dL) Patients with hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV) may receive CAR T-cell products, but they should have undetectable virus before apheresis. In HBV infection, long-term (variably defined, typically 6-12 months) entecavir or tenofovir prophylaxis is recommended, although the possibility of just HBV DNA monitoring in patients with only anti-HBc has been suggested [66]

Summary and Recommendations

Infections are common in patients receiving CAR T cell therapy and cause significant morbidity and mortality. Bacterial infections are the most important cause of severe infection and infection-related mortality. The best strategies to prevent infections are still

being developed. A crucial concept, however, is that CAR T cell recipients are a very heterogeneous group and the individual characteristics of the patient are an important determinant of the infectious risk.

Most severe infections take place during the first few weeks, during neutropenia and coincidentally or closely following CRS. Antibacterial prophylaxis is not generally recommended, but it may be considered on a case-by-case basis. The best use of G-CSF has not been determined, but current guidelines suggest considering it in high-risk patients. CRS severity has been associated with infectious risk in some studies, and corticosteroid treatment consistently so. There is no evidence that tocilizumab increases the risk of infection when given for Grade 1 CRS, but whether it has an impact in other situations remains to be seen.

Prolonged neutropenia is an important risk factor for bacterial infections. Mold infections have also been described in patients with prolonged, profound neutropenia after CAR T Cells [76]

Fungal infections seem relatively rare, and there have been continued arguments about optimal antifungal prophylaxis. [75,77]. Pneumocystis has been seen as a late infection, typically in patients who are not receiving prophylaxis and have low (<200) CD4+ T cell counts.

Upper respiratory viral infections are common and mostly mild. COVID-19, however, has a poor prognosis in CAR T-cell recipients.

Herpes zoster happens mainly in patients who are not receiving acyclovir prophylaxis. CMV infection is uncommon. CMV disease (mainly pneumonia) seems to be rare.

Studies of immune reconstitution show that a significant fraction of CAR T Cell recipients remain profoundly immunocompromised. Anecdotal reports of severe opportunistic infections like toxoplasmosis and HHV-6 serve as a reminder that it is necessary to stay alert for infections for a long time after CAR T infusion.

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