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Infectious events in patients treated with immune checkpoint inhibitors, chimeric antigen receptor T cells, and bispecific T-cell engagers: a review of registration studies

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ABSTRACT

Background: Immunological treatments (immune checkpoint inhibitors [ICIs], chimeric antigen receptor T [CAR-T] cells, bispecific T-cell engagers [BiTEs]) have deeply changed the treatment of several cancers. However, the impact of these treatments on the risk of developing infections has not been completely ascertained yet.

Methods: We reviewed all the registration studies of currently approved ICIs, CAR-T cells, and BiTEs to collect all the reported infections. For each drug, we have generated a report with the infections occurring in at least 10% of the patients enrolled.

Results: The most frequently reported infections involving patients treated with ICIs involved the respiratory tract, including nasopharyngitis, upper respiratory tract infections, and pneumonia and the urinary tract. Those treated with CAR-T cells frequently reported the incidence of unspecified infections and infestations, bacterial infections, and viral infections. In patients treated with BiTEs, nasopharyngitis, pneumonia, and device-related infections were the most frequently reported conditions.

Conclusions: A wide range of infections are reported in registration studies and clinical trials of ICIs, CAR-T cells, and BiTEs.

Introduction

The oncological landscape has been profoundly changed over the last few years due to the availability of new powerful approaches for cancer treatment. Some of these methods act against neoplastic cells, using strategies or targeting aims typical of the immune system. They are therefore defined as immunotherapeutic approaches.

Immune checkpoint inhibitors (ICIs) are drugs that bind to specific proteins (programmed cell death protein 1, PD-1; cytotoxic T-lymphocyte-associated protein 4, CTLA-4; programmed death-ligand 1, PD-L1), overexpressed on T CD8$^+$ cells (PD-1, CTLA-4) or neoplastic tissue (PD-L1) during cancer. These surface markers are called immune checkpoints, in that after binding their cognate antigen they deliver an inhibitory signal leading to a weak and ineffective specific T CD8$^+$ response (Wherry, 2011). ICIs are able to restore the activity of T CD8$^+$ cells against the neoplastic tissue (Pardoll, 2012), providing astonishing results in the treatment of cancers like melanoma, non-small cell lung cancer (NSCLC), and renal carcinoma (Robert, 2020).

Chimeric antigen receptor T cells (CAR-T) consist of T cells that have been manipulated to express chimeric T-cell receptors

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(CARs). These receptors are composed by an extracellular antigen-recognition domain, able to recognize a target antigen, and an intracellular signaling domain, which stimulates T-cell proliferation, cytolysis, and cytokine secretion to eliminate target cells (Jackson et al., 2016). Because the extracellular domain possesses the capacity to recognize intact cell surface proteins, CAR-T cell-mediated targeting of tumors is neither restricted nor dependent on antigen processing and presentation. In addition, CARs can target antigens such as glycolipids, which are aberrantly glycosylated proteins, and conformational epitopes (Feins et al., 2019). Currently, two drugs (axicabtagene ciloleucel and tisagenlecleucel) have been approved by the European Medicines Agency (EMA) and are used in the treatment of B-cell–derived cancers including relapsed/refractory B-cell precursor acute lymphoblastic leukemia, relapsed/refractory diffuse large B-cell lymphoma (DLBCL), after failing of previous treatments (Europena Medicines Agency, n.d., n.d.). Overall, in March 2019, 364 studies evaluating CAR-T cells were ongoing, indicating a really flourishing and promising environment (Xin Yu et al., 2019).

Bispecific T-cell engagers (BiTEs) are recombinant bispecific proteins that have two linked single-chain variable fragments from two different antibodies, one targeting CD3ε, which is an invariable part of the T-cell receptor complex, and the other targeting antigens on the surface of malignant cells (Slaney et al., 2018). Currently, only one drug has been approved by the EMA, blinatumomab, against Philadelphia chromosome-negative CD19-positive relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL) in adult and pediatric patients (EMA - European Medicines Agency, n.d.).

For all these approaches, the evidence in support of the efficacy against certain types of cancer has been well established. What it is unclear is the possible impact on the development of infectious events. Indeed, it is highly likely that these agents can lead to a dysregulation of immune responses with a consequent predisposition to develop or exacerbate infections. Specifically, ICIs restore the action of exhausted T cells, and there is evidence that this could lead to an aggression against latent pathogens, such as *Mycobacterium tuberculosis*, or to an exacerbation of disease manifestations of a concomitant viral infection (ie, chronic hepatitis B, chronic hepatitis C) (Del Castillo et al., 2016a; Fujita et al., 2019; Lombardi et al., 2021; Lombardi and Mondelli, 2019; Picchi et al., 2018a). Recently, these infections have been defined as immunotherapy infections due to dysregulated immunity as opposed to immunotherapy infections due to immunosuppression which are related to immunosuppressant agents (eg, corticosteroids, anti-TNFα agents) used to manage the immune-related adverse event (irAEs) thatcan occurr during ICIs therapy (Morelli et al., 2021). Instead, the approved CAR-T cells and BiTes are all acting toward cells expressing CD19 and thus deplete the organism also from non-neoplastic B cells, which are essential in producing antibodies and cytokines and in the process of antigen presentation.

The aim of this study was to assess the incidence of infectious events reported in the registration studies of the previously defined treatments, to provide an overview of the most common infectious complications.

Methods

The registration studies and clinical trials, including any available associated publication, were examined for infectious adverse events associated with novel checkpoint inhibitors, CAR-T cells and BiTEs therapies. Registration studies data for each drug were obtained from the FDA drug database (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm), and clinical studies leading to approval of each drug were accessed. These studies were searched in two clinical trial databases: NIH Clinicaltrials.gov (https://clinicaltrials.gov) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search). In addition to these registration studies, other clinical trials conducted for each drug were searched by applying four filtering criteria (completed, with results, phase 2, and phase 3) in the same two databases. The search was performed on December 1, 2020.

The following trials were included: nivolumab (NCT02388906, NCT02387996, NCT02181738, NCT02060188, NCT01928394, NCT01721772, NCT01721746, NCT01658878, NCT03371381), pembrolizumab (NCT03950674, NCT02628067, NCT02625961, NCT02576990, NCT02559687, NCT02501096, NCT02453594, NCT02335424, NCT02267603, NCT02256436, NCT02142738, NCT01866319, NCT01848834, NCT01704287, NCT02306850, NCT02337491, NCT02752074, NCT02981524, NCT02351739, NCT02448303, NCT02454179, NCT03211117, NCT02537444, NCT02362048, NCT02690948, NCT02129556, NCT02331368, NCT02959437), ipilimumab (NCT01658878, NCT01673854, NCT01323517, NCT01611558, NCT00162123, NCT01524991, NCT01866319, NCT00623766, NCT02158520, NCT02254772, NCT00323882, NCT01709162, NCT01696045, NCT01471197), atezolizumab (NCT02951767, NCT02108652, NCT02425891, NCT02367781, NCT02924883, NCT02031458, NCT02302807, NCT01846416, NCT01984242, NCT03023423, NCT02729896, NCT02541604), durvalumab (NCT01693562, NCT02125461, NCT02179671, NCT02583477, NCT02401048), axicabtagene ciloleucel (NCT02348216), tisagenlecleucel (NCT02445248, NCT02228096, NCT01747486, NCT01626495, NCT02030847), blinatumomab (NCT01741792, NCT01209286, NCT00560794, NCT02412306).

Occurring infectious adverse events were reported according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. Results were grouped according to severity and/or serious/nonserious scales as reported in the safety data of each trial. Furthermore, infectious adverse events observed in ≥10% of the patients in each clinical trial were grouped together according to the associated drugs to provide a general overview of the events detected. The total number of affected and at-risk patients was calculated to produce a final percentage representing the incidence of these events for each drug.

Results

Infectious adverse events reported in ≥ 10% of all patients enrolled in registration studies and clinical trials of ICIs, CAR-T cells and BiTEs are described in Table 1 . Detailed reports of infections subdivided according to the immunotherapy received and the trial involved are reported in supplementary materials.

Immune checkpoint inhibitors

The most frequently reported infectious events across ICIs involved the respiratory tract, including nasopharyngitis, upper respiratory tract infections, and pneumonia and the urinary tract. Nivolumab was associated with the highest rate of both upper respiratory tract infection and pneumonia, occurring in 20.4% (299/1461) and 15% (12/80) of patients. Regarding urinary tract infections, they are widely represented across ICIs, with the highest prevalence among those receiving ipilimumab (19.6%, 28/143).

Chimeric antigen receptor T cells

Less information could be retrieved from trials on CAR-T cells owing to the lower number of studies performed. Among patients treated with axicabtagene ciloleucel, infections and infestations (26%, 28/108), viral (16%, 17/108), and bacterial infections (13%, 14/108) were reported. Infections developed among patients

Table 1
Infectious adverse events reported in ≥ 10% of all patients enrolled in registration studies and clinical trials of nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, axicabtagene ciloleucel, tisagenlecleucel, and blinatumomab.

Infectious Events	Nivolumab	Pembrolizumab	Ipilimumab	Atezolizumab	Durvalumab	Axicabtagene ciloleucel	Tisagenlecleucel	Blinatumomab
Upper respiratory tract infection[a]	299/1461 (20.4%)	163/1284 (12.7%)	39/327 (11.9%)	153/1321 (11.6%)	70/503 (14.0%)	-	11/73 (15.1%)	-
Pneumonia	12/80 (15.0%)	22/197 (11.1%)	5/40 (12.5%)	2/18 (11.1%)	2/14 (14.3%)	-	-	7/34 (20.5%)
Urinary tract infection	77/637 (12.1%)	302/1973 (15.3%)	28/143 (19.6%)	421/3050 (13.8%)	34/227 (15.0%)	-	-	-
Sinusitis	2/3 (66.6%)	3/25 (12.0%)	6/51 (11.8%)	18/114 (15.7%)	-	-	10/73 (13.8%)	-
Influenza	1/3 (33.3%)	-	5/49 (10.0%)	3/13 (23.0%)	-	-	2/15 (13.3%)	-
Nasopharyngitis	-	126/1085 (11.6%)	5/39 (12.8%)	178/1638 (10.8%)	-	-	-	17/91 (18.6%)
Infections and infestations -Other	-	17/101 (16.8%)	4/36 (11.1%)	-	-	28/108 (26.0%)	147/381 (38.5%)	-
Sepsis	-	1/3 (33.3%)	1/9 (11.1%)	-	-	-	6/60 (10.0%)	3/22 (13.6%)
Bronchitis	-	2/9 (22.2%)	6/42 (14.3%)	1/9 (11.1%)	-	-	-	1/9 (11.1%)
Herpes zoster	1/3 (33.3%)	4/35 (11.4%)	-	-	-	-	-	1/9 (11.1%)
Skin infection	-	2/13 (15.3%)	5/36 (13.9%)	1/10 (10.0%)	-	-	-	-
Rhinitis	-	2/16 (12.5%)	1/8 (12.5%)	12/66 (18.2%)	-	-	-	-
Catheter-related infection	-	1/6 (16.7%)	1/7 (14.3%)	-	-	-	-	4/36 (11.1%)
Conjunctivitis	-	-	1/4 (25.0%)	3/22 (13.6%)	-	-	-	1/5 (20.0%)
Bacterial infection	-	-	-	1/10 (10.0%)	-	14/108 (13.0%)	13/68 (19.0%)	-
Viral infection	-	-	-	1/10 (10.0%)	-	17/108 (16.0%)	18/68 (26.0%)	-
Paronychia	-	1/9 (11.1%)	-	1/9 (11.1%)	-	-	-	-
Diverticulitis	-	-	1/8 (12.5%)	-	-	-	-	1/9 (11.1%)
Cystitis	-	-	1/6 (16.7%)	-	-	-	-	1/9 (11.1%)
Fungal skin infection	-	-	1/8 (12.5%)	1/9 (11.11%)	-	-	-	-
Tonsillitis	-	-	1/8 (12.5%)	1/10 (10.0%)	-	-	-	-
Lung infection	-	1/3 (33.3%)	-	1/2 (50.0%)	-	-	-	-
Oral candidiasis	-	-	-	2/14 (14.0%)	5/20 (25.0%)	-	-	-
Bronchopulmonary aspergillosis	-	-	-	2/20 (10.0%)	-	-	-	1/9 (11.1%)
Device related infection	-	-	-	3/30 (10.0%)	-	-	-	11/75 (14.6%)
Staphylococcal sepsis	-	-	-	1/10 (10.0%)	-	-	-	1/5 (20.0%)
Candida urethritis	-	-	-	1/10 (10.0%)	-	-	-	-
Dermatophytosis	-	-	-	1/3 (33.3%)	-	-	-	-
Genital herpes	-	-	-	1/9 (11.1%)	-	-	-	-
Herpes virus infection	-	-	-	2/19 (10.0%)	-	-	-	-
Postoperative abscess	-	-	-	1/10 (10.0%)	-	-	-	-
Pyelonephritis	-	-	-	2/20 (10.0%)	-	-	-	-
Viral upper respiratory tract infection	-	-	-	1/10 (10.0%)	-	-	-	-
Abdominal abscess	-	-	-	1/10 (10.0%)	-	-	-	-
Cytomegalovirus infection	-	-	-	1/10 (10.0%)	-	-	-	-

(*continued on next page*)

Table 1 (*continued*)

Infectious Events	Nivolumab	Pembrolizumab	Ipilimumab	Atezolizumab	Durvalumab	Axicabtagene ciloleucel	Tisagenlecleucel	Blinatumomab
Laryngitis	-	-	-	1/10 (10.0%)	-	-	-	-
Oral fungal infection	-	-	-	1/10 (10.0%)	-	-	-	-
Pelvic abscess	-	-	-	1/3 (33.3%)	-	-	-	-
Erysipelas	-	-	-	1/10 (10.0%)	-	-	-	-
Bacteremia	-	-	-	2/20 (10.0%)	-	-	-	-
Pharyngitis	-	-	-	8/46 (17.3%)	-	-	-	-
Respiratory tract infection	-	-	-	7/62 (11.3%)	-	-	-	-
Infection (unspecified)	-	-	1/8 (12.5%)	-	-	-	-	-
Rotavirus infection	-	-	1/8 (12.5%)	-	-	-	-	-
Candida nappy rash	-	-	1/8 (12.5%)	-	-	-	-	-
Infected sebaceous cyst	-	-	1/6 (16.7%)	-	-	-	-	-
Diarrhea infectious	-	-	1/6 (16.7%)	-	-	-	-	-
Papulopustular rash	-	-	6/26 (23.9%)	-	-	-	-	-
Neutropenia	-	-	2/9 (22.2%)	-	-	-	-	-
Mastoditis	-	1/8 (12.5%)	-	-	-	-	-	-
Cellulitis	-	5/46 (10.9%)	-	-	-	-	-	-
Staphylococcal	-	-	-	2/20 (10.0%)	-	-	-	-
Diverticulitis	-	-	-	-	1/2 (50.0%)	-	-	-
Fungal infections	-	-	-	-	-	-	9/68 (13.0%)	-
Candida infection	-	-	-	-	-	-	-	2/9 (22.2%)
Gingivitis	-	-	-	-	-	-	-	1/5 (20.0%)
Hepatitis B	-	-	-	-	-	-	-	1/5 (20.0%)
Otitis media	-	-	-	-	-	-	-	1/9 (11.1%)
Gastroenteritis norovirus	-	-	-	-	-	-	-	2/17 (11.7%)

[a] Includes upper respiratory tract infection consisting of viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis

treated with tisagenleucel were slightly different, with infections and infestations occurring in 38.5%, upper respiratory tract infections in 15%, sinusitis in 13.8%, viral infections in 26%, bacterial infections in 19%, and sepsis in 10%.

Bispecific T-cell engagers

The only BiTE that is currently approved for clinical use is blinatumomab and, similar to what was observed for CAR-T cells, a limited number of patients have been enrolled in completed clinical trials. More frequently reported infectious events were nasopharyngitis (18.6%), followed by pneumonia (20.5%), and device-related infections (14.6%).

Discussion

In this study, we provide a complete overview of the infectious events reported in the clinical trials and registration studies of ICIs, CAR-T cells, and BiTEs. Owing to the different number of trials performed, the patients and relative events registered by our study were higher for ICIs compared with CAR-T cells and, particularly, BiTEs. Nonetheless, patients receiving ICIs seemed particularly prone to develop respiratory tract and urinary tract infections, those receiving CAR-T cells showed a peculiar prevalence of infections and infestations and unspecified bacterial/viral infections, and those treated with BiTEs had a high number of device-related infections.

Patients treated with ICIs represent the majority of individuals included in our study. Infections involving the respiratory tract were most frequently reported and were distributed among upper respiratory tract infections, pneumonia, and nasopharyngitis. Interestingly, nasopharyngitis were not reported in patients treated with nivolumab despite being frequent among those receiving pembrolizumab and atezolizumab. It is possible that this condition had been included in the upper respiratory tract infection group, leading to an underestimation. Urinary tract infections are the second most frequently reported group of infections. Overall, these results are in accord with data available in the litera-

ture, where pneumonia, especially of bacterial etiology, was one of the most frequently observed infections (Del Castillo et al., 2016b; Fujita et al., 2019). In general, ICIs are associated with an increased risk of pneumonitis (Su et al., 2019), irAE involving the lungs which are hardly discernible from infectious pneumonia, and it is possible that some of the infections reported in our study can be interpreted as immune-mediated conditions in real-life settings. Intriguingly, in this survey, a relevant number of infections and infestations (16.8%, 17/101) is reported only in patients treated with pembrolizumab, but this could be the consequence of trial design. Finally, despite some studies in the literature suggesting the reactivation of chronic infections (eg, latent tuberculosis) under ICIs treatment (Fujita et al., 2020; Langan et al., 2020; Picchi et al., 2018b), there is no mention of this specific infection among the data analyzed. Currently available guidelines do not highlight an intrinsically increased risk of infections as a consequence of ICI treatment, although they suggest an increased infectious risk in patients developing irAEs who are receiving additional immunosuppressive treatments (Mikulska et al., 2018). Overall, postmarketing surveillance data will be necessary to ascertain the exact incidence of immunotherapy infections due to dysregulated immunity compared with immunotherapy infections due to immunosuppression under ICIs treatment, a knowledge essential to define screening and monitoring programs in this growing group of patients.

Treatment with CAR-T cells is accompanied by a peculiar side effect called cytokine release syndrome which is defined as an acute systemic inflammatory syndrome that is characterized by fever and multiple organ dysfunction, mimicking severe infections (eg, sepsis) (Neelapu et al., 2018). Several possible mechanisms have been identified as responsible for the development of infections among patients treated with CAR-T cells: previous immunosuppression, lymphocyte depleting chemotherapy, treatment of unique toxicities with tocilizumab and steroids, B cell aplasia, hypogammaglobulinemia, and prolonged cytopenia (Bupha-Intr et al., 2021). In our study, the incidence of infection and infestation, bacterial, and viral infection were 26%, 13%, and 16% for those receiving axicabtagene ciloleucel and 38.5%, 19%, and 26% for those treated with tisagenlecleucel, respectively. In the only cohort reporting infections occurring in a real-life experience, among 60 patients with DLCBL treated with axicabtagene ciloleucel and tisagenlecleucel, a total of 101 infectious events were observed, including 25 mild, 51 moderate, 23 severe, 1 life-threatening, and one fatal infection. The cumulative incidence of overall, bacterial, severe bacterial, viral, and fungal infection at 1 year were 63.3%, 57.2%, 29.6%, 44.7%, and 4%, respectively (Wudhikarn et al., 2020). The lower incidence reported in our study was expected, considering the shorter follow-up and the highly selected features of patients enrolled in clinical trials. Treatment with CAR-T cells is relatively new, but preliminary recommendations from scientific societies suggest administering antimicrobial prophylaxis with acyclovir in patients who are seropositive for herpes simplex virus, posaconazole in those at risk for filamentous fungal infection, and fluconazole and cotrimoxazole in all patients, highlighting the significant risk of infectious complications and the need of prevention (Los-Arcos et al., 2020).

With respect to BiTEs, notably, a relevant fraction of patients reported device-related infection. For relapsed or refractory B-ALL, a treatment course consists of up to two cycles for induction, followed by three additional cycles for consolidation treatment, and up to four additional cycles of continued therapy; whereas for minimal residual disease-positive B-ALL, a treatment course consists of one cycle for induction, followed by up to three additional cycles for consolidation (EMA - European Medicines Agency, n.d.). Each induction or consolidation cycle consists of 28 days of continuous IV infusion, followed by a 14-day treatment-free interval between cycles (total 42 days). Continuous infusion requires the presence of an indwelling vascular catheter, and the length of each cycle clearly exposes the patients to the risk of developing catheter colonization and, consequently, catheter-related bloodstream infections (CRBSIs). CRBSIs are typically due to coagulase-negative staphylococci, *S. aureus, Candida* spp., and enteric gram-negative bacilli; they increase length of hospital stay and related costs and can be life-threatening (Mermel et al., 2009). Overall, our data are similar to previously published findings which, next to infections typically found in patients with ALL, also reported higher rates of CRBSI (Mikulska et al., 2018).

Some limitations hamper the results of our study, specifically, the adverse events are reported accordingly to CTCAE v.5.0, with a limited amount of clinical and microbiologic information per event. Moreover, for some molecules, only a few studies have been performed, limiting the conclusions that can be drawn.

In conclusion, a wide range of infections are reported in registration studies and clinical trials of ICIs, CAR-T cells, and BiTEs. ICIs are associated with infections involving the respiratory and urinary tract, CAR-T cells show a high incidence of bacterial/viral infections, and BiTEs are linked to device-related infections. A systematic review of the literature to assess the infectious events reported in patients treated with the molecules is currently ongoing.

Contributors

AL and MUM provided substantial contribution to the design of the study, acquisition, analysis, interpretation of data, and drafted the article; AL and AS contributed to acquisition, analysis, validation, and interpretation of data; AL, AS, RU, GV, and GB acquired, analyzed, and interpreted clinical data and were responsible for data curation; MUM provided substantial contribution to the conception, design of the study, and interpretation of data and revised the manuscript critically for important intellectual content. AL, AG, AB, and MUM supervised the team and had leadership responsibility for the research activity planning and execution and obtained funding. All authors critically read, edited, and approved the final version of the manuscript.

Declaration of Competing Interest

All authors declare no competing of interest.

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Ethical approval was not required.

Supplementary materials

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