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► **To cite this version:**

Jean-Denis Karam, Nicolas Noel, Anne-Laure Voisin, Emilie Lanoy, Jean-Marie Michot, et al.. Infectious complications in patients treated with immune checkpoint inhibitors. *European Journal of Cancer*, 2020, 141, pp.137 - 142. 10.1016/j.ejca.2020.09.025 . hal-03493745

HAL Id: hal-03493745

<https://hal.science/hal-03493745v1>

Submitted on 7 Nov 2022

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Infectious complications in patients treated with immune checkpoint inhibitors

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Count: Abstract: 253 words, Manuscript: 2038 words, 2 tables, 3 figures, 24 references

ABSTRACT

Objective: Immune checkpoint inhibitor (ICI) antibodies constitute a new generation of cancer treatments, associated with immune-related adverse events (irAEs). A previous retrospective study of patients with metastatic melanoma (treated mostly with anti-CTLA4 antibodies) reported a serious infection rate of 7.3%. The main risk factors were corticoids and infliximab use. We sought to describe infections and risk factors among patients receiving anti-PD-1/PD-L1 ICIs.

Patients and Methods: We reviewed 200 medical records sampled randomly from a French prospective registry, which collates patients treated with anti-PD-1/PD-L1 ICIs. We recorded demographic data, the occurrence of irAEs, immunosuppressant use, and the outcome.

Results: Thirty-six patients (18%) experienced an infection by a median [interquartile range] of 47 [19.2-132] days after initiation of the ICI. Twenty-one patients (58.3%) had a lung infection, 7 (19.4%) had a skin infection, 7 (19.4%) had a urinary tract infection, and all of them received antibiotics. The infection were generally mild and treated as outpatient. There were no infection-related deaths, and no opportunistic infection. Sixty percent of the patients were being treated for metastatic melanoma and 35.5% for non-small cell lung cancer, and 106 irAEs (mostly grade 2) were reported. Forty-seven patients received steroids for cancer symptoms or irAEs, and five received immunosuppressants during the immunotherapy. We did not observe any association between corticosteroid or immunosuppressant use and the occurrence of an infection.

Conclusion: The infection rate in patients treated with an anti-PD-1/PD-L1 ICI was 18%, without any severe or opportunistic infection. The occurrence of an infection was not associated with corticosteroid or immunosuppressant use.

Keywords: Cancer immunotherapy; Immune checkpoint inhibitor; Immune related adverse event; Infectious disease; Nivolumab; Pembrolizumab.

(253 words, 1811 characters)

INTRODUCTION

Immune checkpoint inhibitor (ICI) antibodies constitute a new generation of cancer treatments. They have been approved in a growing number of indications, including melanoma, non-small-cell lung cancer, renal cell carcinoma, and Hodgkin's lymphoma[1–5]. However, treatment with ICIs is associated with immune-related adverse events (irAEs) – representing a new challenge for oncologists[6]. The reactivation of auto-reactive T cells can lead to various immune manifestations, such as colitis, pneumonitis, myositis, connective tissue diseases, endocrine disorders, and myocarditis[7]. The incidence of CTCAE grade 3 and 4 irAEs can be as high as 25% for ipilimumab, 10% for single-drug anti-PD-1/PD-L1 treatments, and up to 40% for combination immunotherapies[8–10]; this requires the frequent use of steroids and sometimes even immunosuppressants.

Little is known about the safety of treating irAEs in this context. In particular, data on infections in patients treated for an ICI-associated irAE are scarce. Two studies have been published to date[11,12]. Firstly, Del Castillo et al.'s[11] retrospective study found an odds ratio for infection of 7.71 with corticoid use and 4.74 with infliximab. However, the study population was limited to patients with metastatic melanoma treated predominantly with the anti-CTLA4 antibody ipilimumab. Nowadays, anti-PD-1/PD-L1 immunotherapies are preferred to the anti-CTLA4 approach because they have a better safety profile[13] and are not limited to metastatic melanoma. Secondly, Fujita et al.[12] retrospectively studied lung cancers only, and found that 25 of the 33 reported infections were lung infections. Hence, we decided to assess the frequency of infections documented in a prospective registry of patients treated with anti-PD-1/PD-L1 antibodies for various cancers.

METHODS

The present observational study was based on the REISAMIC prospective registry that collates safety data on all patients treated with ICIs (except for ipilimumab monotherapy) at the Gustave Roussy Institute (Villejuif, France). REISAMIC therefore covers approved indications, institutional clinical trials, and compassionate use. The registry was created on June 1st, 2014, and now holds data on 990 patients and 1029 courses of treatment.

REISAMIC starts to document patients upon the initiation of ICI treatment and stops 3 months after ICI discontinuation or death. We retrospectively reviewed the electronic medical records of 200 patients sampled at random on September 1st, 2018. We collected data on the patient's demographics, the type of cancer, the time since cancer diagnosis, the type and duration of ICI treatment, the cancer treatments prior to ICI use (if any), the occurrence of irAEs, any use of immunosuppressive drugs before or during ICI treatment, antimicrobial treatments, and outcomes.

In order to match routine medical practice as closely as possible, we defined an infection as a prescription of any type of antimicrobial agent by a hospital or a primary care practitioner, with the presence of compatible clinical symptoms and signs (laboratory results and the results of any other assessments, noted in the medical records). Hospitalization, the parenteral administration of antimicrobial agents, and the identification of the pathogenic microorganism were not mandatory criteria. We defined unjustified courses of antimicrobial agents as courses in patients lacking a confirmed or probable diagnosis of infection or with incompatible laboratory and other findings.

ETHICS

The constitution of the REISAMIC registry was authorized by the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés* (Paris, France); registration number: 2098694 V0).

STATISTICAL ANALYSIS

Categorical variables were quoted as the number, (percentage), and continuous variables were quoted as the mean \pm standard deviation, or the median [interquartile range (IQR)]. We compared categorical variables using Fisher's exact test, and continuous variables using the Mann-Whitney U test. To test the putative relationship between infection on one hand and irAEs, the use of immunosuppressive drugs at the time of ICI initiation, the cancer response, and previous treatments on the other, we estimated infection-free survival[14,15] using the Kaplan-Meier method and compared groups using a log-rank test. An event was defined as the occurrence of an infection. Data were censored at ICI withdrawal, death, or loss to follow-up. The threshold for statistical significance was set to $p \leq 0.05$. All statistical analyses were performed using Epi Info™ software (Center for Diseases Control, version 7.2.2.6) and GraphPad PRISM software (version 5.01, GraphPad Software, La Jolla, CA, USA).

RESULTS

Two hundreds patients (108 men, 54%) were assessed. The median [IQR] age was 64 years [53.5-74]. One hundred and twenty patients (60%) had been treated for melanoma, 71 (35.5%) had been treated for non-small-cell lung cancer, and nine (4.5%) had been treated for other cancers (see details in suppl. Table 1). The median follow-up was 143 days [42-294.5]. One hundred and forty-four patients (72%) had received other cancer therapies prior to the index ICI treatment. One hundred and eighty-seven patients (98.5%) were being treated with an anti-PD-1/PD-L1 agent, and three (1.5%) were being treated with a combination of an anti-PD-1 and an anti-CTLA4 agent. At the time of the study, disease progression was observed in 141 patients (70.5%), and only 20 patients (10%) had achieved a complete response (Figure 1A). and stable disease was observed in 32 (16%).

Eighty-four patients reported a total of 106 irAEs (Figure 1B). Most of them affected the endocrine system, the gut, and the skin. Twelve patients experienced two or more irAEs. The irAE severity grade

was CTCAE grade 2 for 50 patients (59.5%), grade 3-4 for 32 patients (38.1%), and grade 5 (death) for 2 patients (2.4%) (Figure 1C).

Eighty-nine patients had received corticosteroids either before the initiation of the index course of ICI and/or for the treatment of irAEs (Figure 1D). Eight patients (4 %) received immunosuppressive drugs (methotrexate in three for pre-existing rheumatic diseases, and in five for treatment of irAEs: three methotrexate and two anti-TNF).

An infection occurred in 36 (18%) patients. The infection sites are summarized in Figure 2. Twenty-one patients (58.3%) had lung infections of suspected bacterial origin (because they were cured with antibiotics). There were no proven cases of pneumocystis pneumonia. Seven patients (19.4%) had a skin infection (erysipelas), 7 (19.4%) had a urinary tract infection, and 1 (2.9%) had an undocumented digestive tract infection. All 36 patients received antibiotics. There were no opportunistic infections, and no infection-related deaths.

The median [IQR] time interval between ICI initiation and infection was 47 days [19.5-132], after a median of 2.3 infusions of ICI. The Kaplan-Meier analyses (Figure 3A) showed that the overall “infection-free” survival rate after ICI initiation was 85.5% at 3 months, 74.8% at 12 months, and 68.4% at 2 years.

In addition to the 36 infections, we found that 30 patients had received an unjustified course of antibiotics. The antibiotics did not resolve the symptoms, and fever and other signs of infection were generally absent. These cases were not considered infections and were excluded from our analyses.

We next compared the 36 patients with an infection with the other 164 patients studied (Suppl Table 2). There were no intergroup differences with regard to age, sex ratio, cancer site, previous and current cancer treatments, the number of ICI infusions received, the cancer response, the incidence of irAEs, the severity of irAEs, and the use of immunomodulatory drugs. A Kaplan-Meier analysis did not reveal a significant difference in infection-free survival with regard to previous chemotherapy or immunotherapy (Figure 3B), or corticosteroid/immunosuppressant use at the time of ICI initiation

(Figure 3C). The cancer response and the presence of an irAE were not associated with a shorter time to infection (data not shown).

DISCUSSION

The present study generated some important information about the occurrence of infections in patients being treated with an ICI[11,12]. We found a higher rate of infections than that reported by Del Castillo et al.; this was partly because our definition of an infection was wider, including outpatient treatment as well as hospitalization. Another interesting difference was that most of the infections observed in the present study were mild; after a median [IQR] follow-up of 143 days [42-294.5], there were no opportunistic infections or infection-related deaths. Identification of the pathogen as a bacterium was based on the effectiveness of antimicrobial prescriptions. Hence, the infection rate observed here might have been an underestimate because we might have missed some nonbacterial infections - especially among the 30 patients having received an unjustified course of antibiotics but whose symptoms were suggestive of an acute but benign viral infection. We wanted our study to match routine medical practice as closely as possible, so our definition of an infection was not too restrictive. However, the definition is certainly open to criticism - at least for diagnoses outside hospital. Furthermore, it is often difficult to distinguish between irAEs and infections (especially pneumonitis and colitis) based on a retrospective analysis of medical records, because the clinical symptoms can be common as the CT scan pictures (thickened bowel wall for example). Moreover, we cannot always establish if the episode was cured by antimicrobials or the immunosuppressive therapy. This is especially the case for pneumonitis because clinicians can prescribe simultaneously antibiotics and steroids in grade 2 pneumonitis, as suggested by Brahmer et al.[16]. Because the immunosuppressive therapies may worsen infections, we advise a quick but thorough search for microorganism documentation before starting immunosuppressants.

The use of antibiotics has been associated with a negative cancer outcome[17–19]. A recent work has suggested antibiotic therapy administered prior to ICI therapy, but not concurrently, was associated

with a worse treatment response and overall survival[20]. Thus, the appropriate use of antimicrobials (with regard to the clinical symptoms and the risk of infection) should be encouraged. This is important because anti-PD1 monotherapy appears to be associated with milder infections and a lower risk of severe infections, relative to combinations of ICIs[11].

The REISAMIC files did not contain details of vaccinations. With a view to limiting antibiotic prescriptions, it is important to vaccinate patients on ICIs against flu[21,22] and pneumococcus (especially if the patients also receive corticosteroids).

In 18 of the 36 patients experiencing an infection (50%), the time to onset was short (less than 47 days after ICI initiation). This new message is relevant for clinicians: patients must be closely monitored during the first weeks of treatment. These early-onset infections contrast with the nature of ICI therapies (designed to enhance immunity) but may reflect T-cell exhaustion present at the initiation of ICI. Prolonged administration of ICIs can indeed improve microbial immunity (as shown for viral infections[23]) and even boost it (as shown for tuberculosis[24]).

In line with Fujita et al.'s study, we found that the use of corticoids and immunosuppressants upon initiation of the ICI was not a risk factor for infections[12]. It is noteworthy that irAEs appeared to be less frequent and less severe in populations where immunosuppressant use is less frequent: the overall frequency of steroid use was 23% in our study as compared with 46% in Del Castillo et al.'s study). This reflects both the heterogeneity of the population studied (i.e. not just patients with metastatic melanomas) and the very high frequency of anti-CTLA4 and combination immunotherapies (associated with a higher risk of irAEs) in Del Castillo's et al.'s population. Moreover, the patients in our study were probably less likely to receive cytotoxic chemotherapy because ICIs now tend to be prescribed earlier in the course of the disease (i.e. as first-line treatments), in view of their effectiveness and good tolerability.

Our study's major strength was its use of our institution's REISAMIC prospective registry; ICI-treated patients with various types of cancer were systematically included and followed up. Although our

study was retrospective, it constitutes the first registry study of infections in ICI-treated cancer patients. Given that the REISAMIC registry collects data on all any irAEs (CTCAE grade ≥ 2) and any other significant adverse events (CTCAE grade ≥ 3), we did not miss any severe infections. However, the heterogeneity of the patients' cancers and adverse events makes it difficult to compare our results with those of other studies. An interesting question could be the occurrence of infections prior to the immunotherapy, in particular for patients who received chemotherapy but the information was not available in the registry. Lastly, the small number of infections limited the power of our statistical analysis.

In conclusion, our results showed that infection remain the major differential diagnosis for irAEs. Eighteen percent of patients treated with an ICI experienced an infection, particularly within the first weeks of therapy and without any clear role for concomitant use of corticosteroids or immunosuppressants.

CONFLICT OF INTEREST STATEMENT

Dr. Olivier Lambotte: paid expert testimony and consultancy fees from BMS France, MSD, AstraZeneca, Incyte; consultancy fees from Genzyme, expert testimony for Janssen.

Dr. Nicolas Noël: speaker fees from MSD and Janssen outside the scope of the submitted work.

Dr. Jean-Marie Michot: fees from Celgene, Bristol-Myers Squibb, AstraZeneca, Janssen. Non-financial support: AstraZeneca, Roche, Novartis, Gilead, Celgene, Bristol-Myers Squibb.

The remaining authors declare no conflicts of interest.

FUNDING SUPPORT

This research did not receive any specific funding from agencies or organizations in the public, commercial, or not-for-profit sectors.

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FIGURE LEGENDS

FIGURE 1. Patients' characteristics summarized

1A. Cancer response at study end (% of the 200 patients)

1B. Immune-related adverse events in 84 patients (n)

1C. CTCAE severity of the immune-related adverse events in 84 patients.

1D. Number of patients receiving immunosuppressants before or during the immunotherapy (n)

FIGURE 2. Distribution of infection sites among the 36 patients.

FIGURE 3.

Kaplan-Meier analyses of infection-free survival following ICI initiation. An event was defined as the occurrence of an infection. Data were censored at ICI withdrawal, death, or loss to follow-up.

A. Overall infection-free survival.

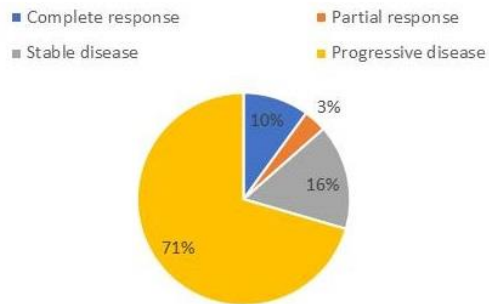
B. Infection-free survival as a function of previous treatments (chemotherapy/immunotherapy, or no treatment).

C. Infection-free survival as a function of the prescription (or not) of corticoids/immunosuppressants upon ICI initiation.

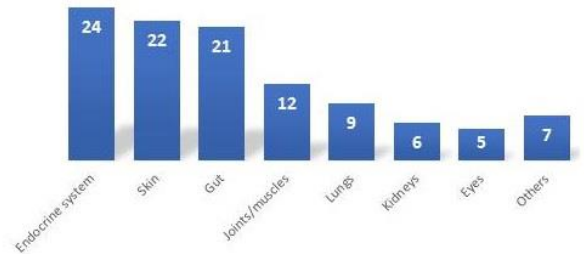
FIGURES

FIGURE 1.

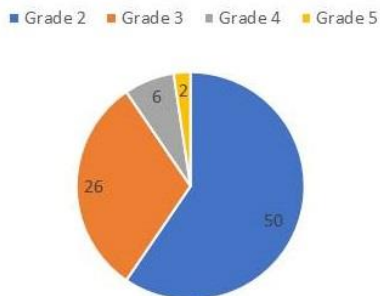
1A Cancer response at study end



1B Immune-related adverse events, (n)



1C CTCAE severity of the irAE in the 84 patients, (n)



1D Patients receiving immunosuppressants, (n)

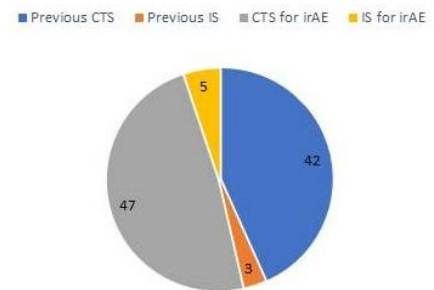


FIGURE 2.

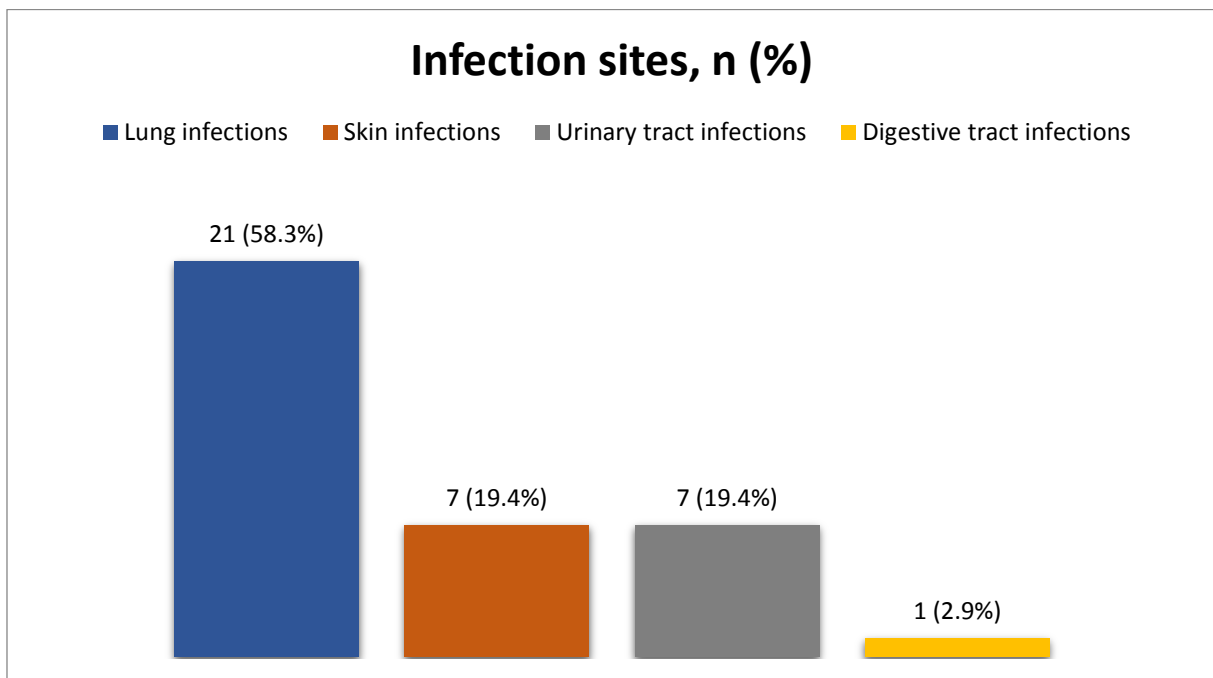


FIGURE 3.

