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Gemcitabine Following Lung Cancer Treatment with Immune Checkpoint Inhibitors: A Potential Risk of *Pneumocystis jirovecii* Pneumonia

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Abstract

Background: Immunocompromised patients are susceptible to severe *Pneumocystis jirovecii* Pneumonia (PJP). The aim of this study is to compare the incidence rate of PJP among patients with solid cancer treated either with gemcitabine after a first-line Immune Checkpoint Inhibitor (ICI) or after a different regimen of anti-cancer treatments.

Methods: Retrospective study of data from patients treated for a solid cancer (mostly lung cancers) and with a diagnosis of PJP, between January 01st, 2017 and June 30th, 2020. We formed four groups of patients: Gemcitabine after ICI (IG group), chemotherapy without prior ICI (C group), chemotherapy other than gemcitabine after ICI (IC group), and ICI just before the diagnosis of PJP (I group).

Results: Among the 210 patients with a microbiologically confirmed diagnosis of PJP, we included 23 patients for whom the diagnosis of PJP was retained: 7 patients in the IG group, 13 patients in the C group, 1 patient in the IC group, 2 patients in the I group. The incidence rate of PCP was significantly higher ($p<0.001$) in the IG group (0.074) compared to the 3 other groups (0.002 in the C group, 0.001 in the IC group and 0.003 in the I group).

Conclusion: The incidence rate of PJP in patients treated for a solid cancer and who received gemcitabine chemotherapy following prior ICI seems significantly higher than among patients who received other treatment regimens. In practice, our work raises the question of the introduction of preventive treatment for PJP in these patients.

Keywords: *Pneumocystis jirovecii* pneumonia; Immune checkpoint inhibitor; Gemcitabine; Bronchoalveolar lavage; Lung cancer

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Abbreviations

PJP: *Pneumocystis jirovecii* pneumonia; ICI: Immune Checkpoint Inhibitor; HIV: Human Immunodeficiency Virus; BAL: Bronchoalveolar Lavage; PCR: Polymerase Chain Reaction

Introduction

Pneumocystis jirovecii Pneumonia (PJP) is responsible for significant mortality in immune-compromised patients, especially HIV patients [1]. It is caused by a ubiquitous fungus called *Pneumocystis jirovecii* [2], an opportunistic pathogen. PJP is far less prevalent among immune-competent patients.

The risk of PJP among HIV patients has greatly decreased since the era of anti-retroviral therapies. For instance, its incidence in Europe dropped from 4.9%/year before 1995 to 0.3%/year after 1998 [3,4]. PJP can also occur in other immunocompromised patients such as solid organ transplant recipients, patients with long-term corticosteroid treatment, and patients with hematological malignancies, solid tumors or auto-immune diseases [3,4]. Among cancer patients, the incidence

of PJP ranges from 0.2% to 0.5% in lymphoblastic leukemia and non-Hodgkin lymphoma patients (higher incidence among hematological malignancies) and 0.1% in patients with solid tumors, and is as high as 0.7% in patients with a brain tumor [5].

The prognosis of PJP is worse in non-HIV patients, with a mortality rate generally estimated to be between 30% and 60% [6], but it can reach 75% in patients requiring mechanical ventilation [7].

The risk of developing PJP can be stratified into 3 groups according to the underlying condition: High risk (>45 cases per 100,000 patient-years) in acute leukemia and chronic lymphoid leukemia for example; intermediate risk (25 to 45 cases per 100,000 patient-years) for central nervous system tumors; low risk (<25 cases per 100,000 patient-years), for other solid tumors [8,9]. Yet PJP risk varies greatly depending on the underlying tumor and resulting treatment.

Immune Checkpoint Inhibitors (ICI) are anti-PD-1, anti-PD-L1, and anti-CTLA-4 monoclonal antibodies that are increasingly used for the treatment of solid tumors, either alone or in combination with chemotherapy. Chemotherapy has a direct cytotoxic effect, but can also trigger an immunogenic cell death in conjunction with the patient's immune response, including cytotoxic T lymphocytes [10-13].

Since the introduction of ICI as second and then a first-line treatment for non-small-cell lung cancer, several patients have been admitted to our tertiary respiratory intensive care unit presenting severe PJP after treatment for lung cancer with gemcitabine following an ICI, and with no history of HIV infection. We frequently use gemcitabine after ICI because one study has shown a better objective response rate (ORR=63.6%) [14]. Moreover, gemcitabine has less adverse effects compared to taxanes, for example, which cause disabling neuropathies in patients who are already in poor general condition.

Considering the role of the lymphocyte-mediated immune response against *Pneumocystis jirovecii*, these case series led us to reflect on the risk of developing PJP in the course of chemotherapy treatment (and in particular following gemcitabine) after a prior line of ICI.

We thus aimed to compare the incidence rate of PJP among patients with solid cancer treated either with gemcitabine after a line with an ICI or after a different regimen of anti-cancer treatments. The objective was also to study the characteristics of these patients and to assess whether gemcitabine or ICI could have a role in the development of PJP.

Material and Methods

Population

Patients with a microbiologically confirmed diagnosis of PJP (either a positive polymerase chain reaction or the presence of *Pneumocystis jirovecii* cysts on direct examination) between January 01st, 2017, and June 30th, 2020. Data were retrospectively retrieved from the registry of the Dijon University Hospital's Parasitology and Mycology Department. Each case was examined to assess whether patients had been treated with ICI and/or chemotherapy for a solid tumour in our hospital or in the Georges Francois Leclerc Cancer Centre (CGFL) (Dijon, France). Patients treated for a hematological malignancy were excluded.

Patients were classified into 4 groups: Those who had received ICI followed by gemcitabine (IG group), those who had received only chemotherapy (C group), those who had received ICI followed by chemotherapy other than gemcitabine (IC group), and those who had received ICI just before the diagnosis of PJP (I group).

PJP diagnosis

The biological diagnosis was based on either induced sputum or Bronchoalveolar Lavage (BAL) samples. The presence of *P. jirovecii* was assessed on direct examination and/or using a quantitative PCR (qPCR). The patients were included if their clinician had confirmed a diagnosis of PJP based on a positive biological test associated with a compatible clinical and radiological presentation.

Incidence rate

We calculated the incidence rate for each group using the total number of patients who underwent chemotherapy, following ICI treatment or not, for a solid tumour at the Dijon University Hospital or CGFL during the study period. The incidence rate of PJP in each group was calculated by dividing the number of PJP cases by the total number of patients treated with the same therapeutic sequence during that period.

Medical characteristics

We collected the following data for each patient: Demographic characteristics (age, sex, body mass index), past medical history (respiratory diseases, hematological malignancy, solid tumors, HIV status, solid organ transplant, smoking history), concomitant treatments (immunosuppressive drugs, including corticosteroids - mean dose over the last 30 days), specific oncologic status (tumor type, recent surgery or radiotherapy, chemotherapy or ICI regimen, total number and time after the last round of treatment), imaging characteristics (aspect of the PJP on imaging, evolution under specific treatment), blood sample results (CRP, PCT, FBC, Beta D-glucan, mannan antigen and antibodies, serum albumin), microbiological data (respiratory sample type, qPCR cycle number, BAL characteristics), and PJP-specific treatment and outcome.

Case control study

To investigate the presence of confounding factors, we also performed a case-control study in patients with lung cancer.

A case was defined as a patient with a diagnosis of PJP (a positive biological test associated with a compatible clinical and radiological presentation). Controls were randomly selected among the patients followed in our hospital or at the CGFL. The ratio was 1:3. All cases and controls were being followed for non-small cell lung cancer. Exposure information (gemcitabine following ICI or other oncologic treatment) was collected through a specialized prescription software for cancer treatment (Chimio by Computer Engineering).

Statistical analysis

Descriptive statistics for continuous variables are presented as means and standard deviations or medians and inter-quartile ranges (25% to 75%). For the comparison of incidence rates, a p-value <0.05 is considered significant.

The crude relationship between chemotherapy and occurrence of pneumocystosis was estimated in univariate analysis using Fisher's exact test and a univariate logistic regression model. An adjustment taking into account the following potential confounding factors was made: Corticosteroid therapy (mean dose over the last 30 days), level of lymphocytes, age, and sex. A multiple logistic regression was

used; with a robust variance estimator. Log linearity was checked using fractional polynomials. Model discrimination was assessed through the area under the ROC curve. Model calibration was assessed using the Hosmer-Lemeshow test. Internal validity was estimated by bootstrap (with 100 replications). Finally, a sensitivity analysis was performed using a Bayesian approach. Convergence was checked. Stata software, version 15 was used for all analyses, which were performed by a senior statistician from the Epidemiology and Hospital Hygiene Department at the Dijon University Hospital.

Results

Population

Among 210 patients with a direct examination and/or a PCR positive for *Pneumocystis jirovecii* between January 01st, 2017, and June 30th, 2020, 23 patients met the inclusion criteria (Figure 1). Seven patients received ICI followed by gemcitabine chemotherapy (IG), 13 received a chemotherapy without prior treatment with ICI (C), 1 received an ICI followed by chemotherapy other than gemcitabine (IC), and 2 received ICI before the PJP diagnosis (Table 1).

The IG group was composed of all men, and the mean age was 62.3 years. All of them were treated for a lung adenocarcinoma, and one of them was also treated for a synchronous small cell lung cancer. In the C group, the mean age was 68.9 years, and there were 7 women and 6 men. Four patients were treated for a lung cancer (1 squamous cell lung cancer, 3 lung adenocarcinoma), one for a thymic carcinoma, 5 for breast cancer and 3 for digestive cancer. In the IC group, the patient was 75 years old, and had been treated with nivolumab then paclitaxel for a squamous cell lung cancer. The I group was composed of all women, and the mean age was 66.4 years. One was treated for a squamous cell lung cancer, the other for a malignant melanoma.

Sixteen out of 23 patients (69.6%) were treated with corticosteroids over the last 30 days before diagnosis, 6 out of 7 in the IG group (86%), 9 out of 13 in the C group (69.2%), 1 out of 1 in the IC group (100%) and 1 out of 2 in the I group (50%). The mean dose of corticosteroids over the last 30 days before diagnosis (in prednisone equivalent) was 32.2 mg/day in the IG group, 28.2 mg in the C group, 24 mg/j in the IC group and 4.5 mg in the I group.

No patient was being treated with an immunosuppressive drug other than corticosteroids at the time of the diagnosis and only one patient received prophylaxis for PJP.

Table 2 presents the characteristics of the respiratory samples, the qPCR cycle count and the cell analysis of the BAL.

Incidence

The incidence rate of PJP was calculated with the number of cases in each group divided by the total number of patients treated by the same regimen during the same time period. The rate was 0.074 (7/95 patients) in the IG group, 0.002 (13/6098 patients) in the C group, 0.002 (1/619 patients) in the IC group and 0.003 (2/690 patients) in the I group. The incidence rate of PJP was significantly higher in the

Table 1: Baseline patient characteristics.

	Total n=23	IG group n=7	C group n=13	IC group n=1	I group n=2
Age - yrs (mean)	67.0 ± 11.6	62.3 ± 16.7	68.9 ± 9.2	75.2	66.4 ± 2.0
Gender					
Female - nº (%)	9 (39.1)	0 (0)	7 (53.8)	0 (0)	2 (100)
Male - nº (%)	14 (60.9)	7 (100)	6 (46.2)	1 (100)	0 (0)
Body mass index - kg/m² (mean)	24.4 ± 5.8	23.4 ± 4.9	23.4 ± 5.3	19.1	31.3 ± 11.2
OMS performance status (mean)	1.9 ± 0.8	2 ± 1	1.8 ± 0.8	3	1.5 ± 0.7
History of tobacco use					
Never smoker - nº (%)	7 (30.4)	1 (14.3)	5 (38.5)	0 (0)	1 (50)
Former smoker - nº (%)	14 (60.9)	5 (71.4)	7 (53.8)	0 (0)	1 (50)
Current smoker - nº (%)	2 (8.7)	1 (14.3)	0 (0)	1 (100)	0 (0)
N/A- nº (%)	1 (4.3)	0 (0)	1 (7.7)	0 (0)	0 (0)
Pack-years (mean)	19.2 ± 20.6	28.1 ± 18.4	12.5 ± 18.0	10	30 ± 42.4
PJP risk factors					
Respiratory disease - nº (%)	7 (30.4)	4 (57.1)	2 (15.4)	0 (0)	1 (50)
Solid organ transplant - nº (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Haematological malignancy- nº (%)	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (50)
Inflammatory diseases - nº (%)	2 (8.7)	0 (0)	0 (0)	0 (0)	2 (100)
Another associated solid tumour - nº (%)	5 (21.7)	3 (42.9)	1 (7.7)	1 (100)	0 (0)
HIV - nº (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immunosuppressive drugs					
Corticosteroid - prednisolone dose-equivalence mg (mean)	27.2 ± 28.2	32.2 ± 29.7	28.2 ± 30.2	24	4.5 ± 6.4
Other immunosuppressive drugs - nº (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PJP prophylaxis - nº (%)	1 (4.3)	1 (14.3)	0 (0)	0 (0)	0 (0)

Group IG: patients who had received gemcitabine after ICI
Group C: patients who had received a chemotherapy without prior ICI
Group IC: patients who had received a chemotherapy other than gemcitabine after ICI
Group I: patients who had received ICI just before the diagnosis of PJP

Table 2: Characteristics of respiratory samples.

	Total n=23	IG group n=7	C group n=13	IC group n=1	I group n=2
Sample type					
Induced sputum - nº (%)	4 (17.4)	4 (57.1)	0 (0)	0 (0)	0 (0)
BAL - nº (%)	19 (82.6)	3 (42.9)	13 (100)	1 (100)	2 (100)
PCR cycle count (mean)	32.1 ± 3.9	36.7 ± 12.6	31.2 ± 3.4	38	36 ± 2.8
Cell count					
Total cell count - cells/mm³ (median)	297 (180-1039.5)	297 (269.5-3273.5)	420 (160-972)	990	13
Neutrophils - % (median)	58 (21.5-88)	58 (55.5-72.5)	28.5 (11.5-86.75)	73	90
Eosinophils - % (median)	0 (0-1)	0 (0-1)	0(0-1)	0	0
Basophils - % (median)	0	0	0	0	0
Lymphocytes - % (median)	6 (2-22)	6 (4-13.5)	7 (2.25-34.25)	7	1
Macrophages - % (median)	20 (10-34.5)	26 (18.5-30)	25 (10-53.75)	20	9
Mast cells - % (median)	0	0	0	0	0
Association with other pathogens - nº (%)	14 (60.9)	4 (57.1)	8 (61.5)	0 (0)	2 (100)

BAL: Bronchoalveolar Lavage

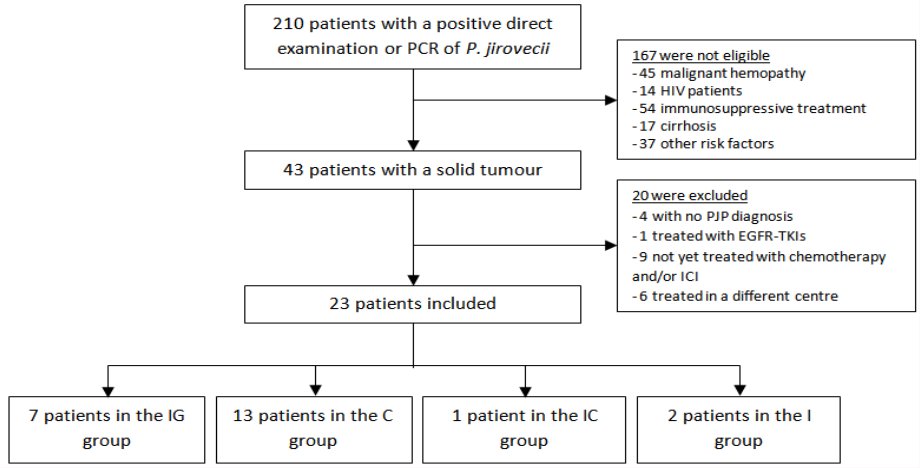

Figure 1: Flow-chart.

Table 3: PJP management and prognosis.

	Total n=23	IG group n=7	C group n=13	IC group n=1	I group n=2
Outpatient - nº (%)	1 (4.3)	0 (0)	1 (7.7)	0 (0)	0 (0)
Hospital ward - nº (%)	5 (21.7)	2 (28.6)	2 (15.4)	0 (0)	1 (50)
Intensive care unit - nº (%)	17 (73.9)	5 (71.4)	10 (76.9)	1 (100)	1 (50)
Fatal PJP rate - nº (%)	13 (56.5)	3 (42.9)	8 (61.5)	0 (0)	2 (100)

IG group compared to the 3 other groups (p<0.001) (Table 3).

Median time interval between the initiation of treatment and the diagnosis of PJP

The median time interval between the first round of the last treatment regimen and the diagnosis of PJP was 52 days in the IG group, 166 days in the C group, 65 days in the IC group and 316 days in the I group (Figure 2).

Medical care

The vast majority of patients were treated in intensive care units. The PJP-related mortality rate was 42.9% in the IG group, 61.5% in the C group, 0% in the IC group and 100 % in the I group. The single patient in the IC group was treated in intensive care unit and survived.

Case control study

42 patients were recruited: 12 cases (7 in the exposed group and 5 in the not exposed group) and 30 controls (15 in each group). There was no relationship between exposure (gemcitabine following ICI) and occurrence of PJP (Fischer's exact test =0.738).

Adjustments were made in a univariate model taking into account the following potential confounding factors: No relationship between exposure and PJP adjusting it on corticosteroid therapy (p=0.275), level of lymphocytes (p=0.871), sex (p=0.856), there is a relationship between exposure and PJP adjusting it on age (p=0.001).

Adjustments were made in a multivariate model taking into account the following potential confounding factors: No relationship between exposure and PJP adjusting it on corticosteroid therapy

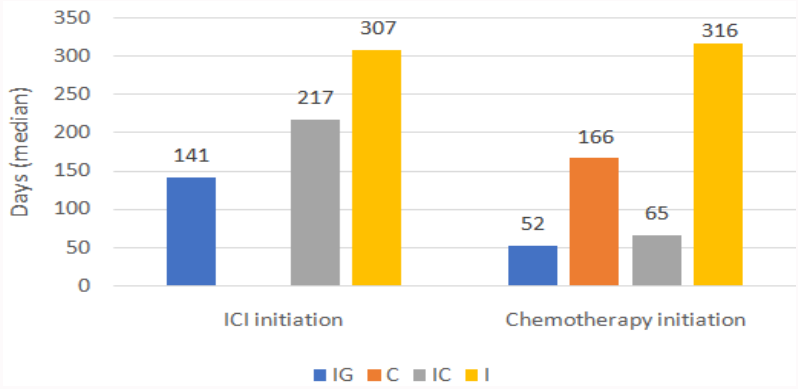

Figure 2: Median time interval between the initiation of treatment (chemotherapy or ICI) and the diagnosis of PJP.

(p=0.092), level of lymphocytes (p=0.885), sex (p=0.662), there is a relationship between exposure and PJP adjusting it on age (p=0.003).

Discussion

Our results suggest that patients treated for a solid tumour and who received gemcitabine chemotherapy following treatment with ICI have a significantly higher incidence rate of PJP compared to patients who follow other treatment regimens (p<0.001).

In the literature, few cases of PJP are reported after chemotherapy with gemcitabine or after ICI. Schwarz et al. [15] reported 2 cases in non-small-cell lung cancer patients receiving corticosteroids after an episode of immune-related pneumonia. Another case was reported after pembrolizumab for a hematological malignancy [16]. In a similar series of PJP after chemotherapy with gemcitabine, Lingartnam et al. [17] found an incidence rate of 3.1% (9 out of 288 patients) with a median time interval between gemcitabine initiation and the diagnosis of PJP of 67 days. In our series, we found a slightly shorter time interval of 52 days.

The case-control study did not reveal a relationship between the disease (PJP) and exposure (gemcitabine following ICI). We chose to include only patients with lung cancer to focus on the population of patients we follow on a daily basis. The lack of relationship can be explained by the small sample size (12 cases and 30 controls). However, the case-control study showed that, in our sample, corticosteroid therapy and lymphocyte counts were not confounding factors.

The individual role of CD4+ and CD8+ lymphocytes in the immune response against *P. jirovecii* is uncertain. In a murine model, Bhagwat et al. [18] studied the interaction between different T cell subtypes during PJP, and how each subtype may play a different role in the clearance of the fungus, the inflammatory lesions or the resolution phase of inflammation. They show that the clearance of *P. jiroveci* and the intensity of the overall inflammatory response depend on the balance between CD4+ and CD8+ T cells. An appropriate balance results in a faster clearance with minimal lung inflammation and no apparent clinical disease. When there is a relative excess of CD8+ T cells (as seen in patients undergoing chemotherapy), non-protective and pathological inflammation occurs with more lung injury and a differed clearance of the infection. This CD8+ oriented T cell response might be further boosted by the use of ICI.

During ICI treatment, the PD-1 or PD-L1 inhibition enhances the CD8+ T cell effector function, providing more effective anti-tumour activity. The subsequent gemcitabine chemotherapy has immune effects, but with different mechanisms: inhibition of immunosuppressive cells such as myeloid suppressor cells [19-22], and activation of dendritic cells. Gemcitabine can also increase gamma interferon producing T cell and CD69+ cell recruitment [23,24].

The depletion of myeloid suppressor cells enhances the effector functions of CD8+ T cells [25]. This could lead to an excessive CD8+ immune response to *P. jirovecii* if present in the lungs during this treatment, causing bystander inflammatory lesions and a poor clearance of the fungus.

This improvement in CD8+ T cell activity with chemotherapy following ICI treatment has been studied [26,27]. The objective response rate to chemotherapy is improved after ICI treatment in several chemotherapy regimens [14]. This improvement seems to be particularly important with gemcitabine due to its effects on tumor microenvironment [28-30].

Though there are numerous causes for immunosuppression among oncology patients, high dose and/or long-term corticosteroids area well-known risk factor of PJP [31,32]. Surprisingly, the use of a prophylactic treatment in solid tumour patients is far less common than in patients with hematological malignancy or than in HIV patients, even though it has been proven to be efficient [33-35]. This may be explained by the lack of recommendations for these patients. Based on retrospective studies and expert consensus, some studies have proposed the use of PJP prophylaxis under certain conditions (CD4+ T cells <200/mm^3, more than 20 mg/day of systemic prednisolone equivalent for more than 4 weeks) [5,17,36-38].

Direct lung toxicity under gemcitabine or ICI treatment has been reported, ranging from mild dyspnea to an acute respiratory distress syndrome [39,40]. The clinical (cough, fever, dyspnea) and radiological (interstitial opacities) presentation can be similar to that of a PJP. This potential diagnosis must thus be raised and investigated, using BAL lavage or alternatively induced sputum.

This study has some limitations. Its retrospective nature made difficult to assess some factors such as concomitant treatments, and made it more difficult to get an exhaustive list of the cases. Nonetheless, using the laboratory and pharmacy registries, we were able to minimize the risk of missed cases. The limited number of cases found in the two participating centers also limited the statistical analyses. A larger study including more centers could help in that regard. The role of the systemic corticosteroid treatment is also a

potential bias, which is hard to manage in this retrospective study. To overcome this bias, we performed an additional case-control study focusing on lung cancer. Both univariate and multivariate analysis found that corticosteroid therapy was not a significant confounding factor.

Conclusion

In conclusion, the incidence rate of PJP in patients treated for a solid tumour and receiving chemotherapy with gemcitabine after a previous line of treatment with ICI was significantly higher than in any other treatment course. The search for other risk factors such as corticosteroid treatment should be systematic. This could have implications in daily practice, for instance resulting in the potential use of a prophylactic therapy with cotrimoxazole or the need for a systematic assessment of a *P. jirovecii* colonization when lung cancer patients undergo an endoscopy. These data strongly support systematic investigations for PJP in patients presenting acute respiratory distress syndrome in the course of a treatment that includes gemcitabine chemotherapy after an ICI.

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