Increased reporting of fatal pneumonitis associated with immune checkpoint inhibitors: a WHO pharmacovigilance database analysis

To the Editor:

The discovery of immune checkpoint inhibitors (ICIs), which include anti-programmed cell death protein-1 (PD-1), its ligand (PD-L1) and anti-cytotoxic T cell lymphocyte-associated protein-4 (CTLA-4), has transformed the field of oncology, with indications continuing to increase. For example, anti-PD1 and anti-CTLA-4 ICIs, which include nivolumab, pembrolizumab and ipilimumab, are US Food and Drug Administration/European Medicines Agency approved for a variety of cancers, such as melanoma and non-small cell lung carcinoma (NSCLC) [1]. Considered the Achilles' heel of ICIs, however, are immune-related adverse events (irAEs) (10–60% high grade) that represent an inflammatory response that can affect multiple organ systems, which can be fatal (0.3–1.3%) [2].

Among these irAEs is ICI-related pneumonitis, which is a serious adverse event with reports of up to 1% to 4% of patients on ICI monotherapy and 4% to 7% on combination therapy [3, 4]. Most of the available data were derived from clinical trials that may not be representative of a real-world population and settings. As such, reports of ICI-pneumonitis in the international pharmacovigilance database, Vigibase, were retrospectively reviewed to characterise their main features and factors associated with death.

Our study is a descriptive analysis based on adverse drug reactions (ADR) reported within VigiBase, the World Health Organization global deduplicated individual case safety reports (ICSRs) database, originating from more than 130 countries [5–7]. VigiBase contains over 18 million ICSRs submitted by national pharmacovigilance centres since 1967. These reports mainly originate from real-life populations with different sources, including healthcare professionals, patients and pharmaceutical companies. The use of confidential electronically processed patient data was approved by the French National Commission for Data Protection and Liberties (reference: 1922081). This study is part of NCT03492242 [5–7].

We performed a search for ADRs associated with anti-CTLA-4, anti-PD1, anti-PD-L1, and their combinations. We searched all ICI-pneumonitis according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) using the preferred term "pneumonitis", up to 4 November, 2018. ICI-pneumonitis specifically considered in the analysis were those reported as "suspected" secondary to ICI. Demographic and clinical data were collected and reviewed. Characteristics of cases were described in terms of mean±SD or medians (with interquartile ranges (IQR)) for quantitative variables, and in terms of effective and proportion for qualitative ones. To compare fatal *versus* non-fatal pneumonitis, unpaired t-test, Mann-Whitney and χ^2-tests were calculated, as appropriate (*R-software*).

Between inception through November 04, 2018, a total of 1694 ICI-pneumonitis were identified with a marked increase in reporting of ICI-pneumonitis of approximately 4 cases per month between 2010 and 2014 to 71 cases per month in 2018. The majority of cases originated from North America (47.5%) and Europe (39.8%) and were reported predominantly by healthcare providers (n=1277/1545, 82.7%) in a non-clinical trial setting (n=1596/1619, 98.6%). Patients with ICI-pneumonitis were mostly men (n=946/1694, 63.6%) with a median age of 65 years (range 7–103; n=1130/1694). Patients mainly received ICI for lung cancer (55.9%, n=776/1388) and melanoma (22.1%, n=307/1388). There were 88.1% (n=1492/1694)

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There was an increased reporting of immune checkpoint inhibitor (ICI)-pneumonitis over the past few years with earlier time to onset of fatal ICI-pneumonitis, which was associated with more respiratory failure and tumour progression http://bit.ly/32GW51a

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of patients who received ICI monotherapy (71.8% anti-PD1, 10.6% anti-PD-L1 and 5.7% anti-CTLA-4) and 11.9% (n=202/1694) combination therapy (mainly anti-CTLA-4 and anti-PD1). ICI were the only suspected drug inducing pneumonitis in 87.7% (n=1486/1694) of the cases. Time to onset (TTO) was available in 336/1694 (19.8%) patients. In these patients, median TTO of ICI-pneumonitis was 43 days (range 0–3345). Concurrent irAEs occurred in 390/1694 (23.0%) patients, mainly represented by gastrointestinal (29.2%, n=114/390) and endocrine (24.9%, n=97/390) irAEs.

In our analysis, serious adverse events, defined by life threatening, prolonged hospitalisation or physical disability were observed in all cases, leading to death in 297/1694 (17.5%) of ICI-pneumonitis cases. There were no significant differences in gender, age, country of reporting, reporter type (healthcare, non-healthcare professional), setting (clinical, non-clinical trial setting) and year of reporting (starting 2011 and ending 2018) for fatal *versus* non-fatal ICI-related pneumonitis cases (table 1).

There were no preferential seasons for the onset of fatal ICI-pneumonitis (p=0.54). There was increased report in ICI-pneumonitis deaths with an average of 10 cases per month in 2017–2018 *versus* 1 case per month between 2010 and 2014. Use of ICI combination *versus* ICI monotherapy and type of monotherapy (anti-PD1, anti-PD-L1 and anti-CTLA4) were similar in fatal *versus* non ICI-pneumonitis cases (table 1), but fatality was increased in patients with lung cancer (60.3%, 158/262 *versus* 54.9%, 618/1126) compared to melanoma (14.9%, 39/262 *versus* 23.8%, 268/1126;, p=0.0003). Within anti-PD1 monotherapies, fatality was not different per ICI dosage (p=0.58); however, it was higher among pembrolizumab *versus* nivolumab treated patients (22.4%, 92/411 *versus* 15.7%, 126/805, respectively; p=0.004; n=54/185 *versus* 17.5%, n=80/456; p=0.001 in lung cancer subset).

TTO was statistically different between fatal and non-fatal cases with fatal ICI- pneumonitis cases occurring with a shorter TTO than non-fatal cases (median 24 days (IQR 12–41 days) *versus* 53 days (IQR 21–132.75), respectively; p<0.0001). To further categorise ICI-pneumonitis, we determined concomitant conditions. Concomitant irAEs were identified in 26.2% (n=78/297) of fatal ICI-pneumonitis ICSRs and included colitis (8.1%, n=24/297) and dermatitis (6.7%, n=20/297) among others. There was 29.8% (n=505/1694) of all ICI-pneumonitis cases with other conditions (table 1). Concomitant conditions were associated with 52.9% (n=157/297) of fatal ICI-pneumonitis, which were sepsis-related in 26.8% (n=42/157) of cases. Fatal cases were associated with more respiratory failure, thromboembolism and tumour progression (table 1).

To our knowledge, this study represents the largest international description and characterisation of ICI-pneumonitis cases to date. We observed a significant increase of ICI-pneumonitis with unchanged fatality rate over years. We observed an earlier TTO for fatal ICI-pneumonitis *versus* non-fatal cases which emphasises the need for understanding the biological mechanisms, identifying any risk factors and temporalities that can aid in the diagnosis and effective management in these patients.

A meta-analysis comparing ICI *versus* conventional chemotherapy in randomised controlled trials (n=7246 patients) found a significantly higher risk of high-grade and all-grade ICI-pneumonitis (OR 4.39, p=0.003 and OR 2.46, p=0.007, respectively) in the ICI treatment arm [8]. In comparison to dermatological or endocrine-irAEs which may be linked to better prognosis [9], in lung cancer, ICI-pneumonitis accounted for 35% of anti-PD1 and anti-PD-L1-related deaths [10–12]. In our study, we observed a higher incidence of ICI-pneumonitis which is suspected due to a combination of increase use of ICI and awareness of irAEs. Fatal ICI-pneumonitis cases were also seen in lung cancer patients, which has been suggested to be a result of multiple factors including effect of radiation synergy and a pulmonary tumour burden affecting the microenvironment and inflammatory response [3, 4, 13].

Similar to previous literature, there is a wide range of TTO to ICI-related pneumonitis which may be affected by common overlapping symptoms and radiographic features that may mimic underlying pulmonary conditions such as concomitant obstructive or restrictive lung disease, pulmonary infections but also lung cancer progression/hyperprogression, and a lack of consensus terminology to specifically describe and define ICI-related pneumonitis [3, 4, 14]. Early diagnosis aided by radiographic evidence would be pivotal for immediate management since fatality from ICI-related pneumonitis can occur earlier in the treatment course as observed in our study. For example, obtaining chest computed tomography (CT) prior to the second ICI administration could be of utility in order to monitor for the presence or development of specific pulmonary radiographic findings, such as ground-glass opacities/patchy consolidations, before the onset of respiratory symptoms and/or failure. Chest CT surveillance should also be strongly considered, especially in patients treated for lung cancer receiving pembrolizumab and/or with respiratory comorbidities to identify concomitant infection and early cancer hyperprogression [15].

Although this is the largest description of ICI-related pneumonitis to date, there are limitations to the study. First, the absolute incidence of ICI-related pneumonitis cannot be assessed because VigiBase does

TABLE 1 Main characteristics of fatal *versus* non-fatal pneumonitis associated with immune checkpoint inhibitors (ICIs) in VigiBase through November 04, 2018

	Fatal pneumonitis (297/1694 cases)		Non-fatal pneumonitis (1397/1694 cases)		p-value
	n (%)	Available data	n (%)	Available data	
Males	178 (65.9%)	270/297 (90.9%)	768 (63.0%)	1218/1397 (87.2%)	NS
Age years	65 [56–71] (7–100)	213/297 (71.7%)	65 [56–71] (18–103)	917/1397 (65.6%)	NS
Country region					
North America	155 (52.2%)	297/297 (100%)	650 (46.5%)	1397/1397 (100%)	NS
Europe	123 (41.4%)		552 (39.5%)		
Asia	14 (4.7%)		116 (8.3%)		
Africa	4 (1.4%)		4 (0.29%)		
South America	1 (0.3%)		9 (0.64%)		
Notifier type					
Healthcare professional	212 (80.3%)	264/297 (88.9%)	1065 (83.14%)	1281/1397 (91.7%)	NS
Non-healthcare professional	52 (19.7%)		216 (16.86%)		
Report type					
Non-clinical trials	288 (98.6%)	292/297 (98.3%)	1284 (96.8%)	1327/1397 (95.0%)	NS
Clinical trials	4 (1.4%)		43 (3.2%)		
Reporting year					
2018	113 (38.0%)	297/297 (100%)	590 (42.2%)	1397/1397 (100%)	NS
2017	103 (34.7%)		465 (33.3%)		
2016	52 (17.5%)		209 (14.9%)		
2015	18 (6.1%)		97 (6.9%)		
2011–2014	9 (3.7%)		25 (1.9%)		
Days to onset	24 [12–41] (0–200)	35/297 (11.78%)	53 [21–132.75] (0–3345)	301/1397 (21.55%)	<0.0001
Season					
Winter	29 (28.7%)	101/297 (34.0%)	134 (25.8%)	520/1397 (37.2%)	NS
Spring	26 (25.7%)		143 (27.5%)		
Autumn	23 (22.8%)		104 (20.0%)		
Summer	23 (22.8%)		139 (26.7%)		
ICI monotherapy *versus* combination					
Monotherapy	266 (89.56%)	297/297 (100%)	1226 (87.76%)	1397/1397 (100%)	NS
Combination	31 (10.44%)		171 (12.24%)		
ICI types					
PD1 inhibitor alone	218 (73%)	297/297 (100%)	999 (72%)	1397/1397 (100%)	NS
PD-L1 inhibitor alone	33 (11%)		146 (10%)		
CTLA4 inhibitor alone	15 (5.1%)		81 (5.8%)		
ICI monotherapy					
Atezolizumab (PD-L1)	22 (7.4%)		69 (4.9%)		0.007
Avelumab (PD-L1)	2 (0.7%)		3 (0.2%)		
Durvalumab (PD-L1)	9 (3.0%)		74 (5.3%)		
Nivolumab (PD1)	126 (42.4%)		679 (48.6%)		
Pembrolizumab (PD1)	92 (31.0%)		319 (22.8%)		
Ipilimumab (CTLA-4)	15 (5.1%)		80 (5.7%)		
Tremelimumab (CTLA-4)	1 (0.3%)		1 (0.1%)		
ICI combination therapy					
Nivolumab+ipilimumab	29 (9.8%)		151 (10.8%)		NS
Durvalumab+tremelimumab	1 (0.3%)		9 (0.6%)		
Other combination	1 (0.3%)		9 (0.6%)		
ICI indications					
Lung	158 (60.3%)	262/297 (88.2%)	618 (54.9%)	1126/1397 (80,6%)	<0.0001
Melanoma	39 (14.9%)		268 (23.8%)		
Kidney	6 (2.3%)		68 (6%)		
Urothelial and bladder	8 (3.1%)		31 (2.8%)		
Lymphoma	9 (3.4%)		27 (2.4%)		
Head and neck	7 (2.7%)		20 (1.8%)		
Other	35 (13.4%)		94 (8.3%)		

Continued

TABLE 1 Continued

	Fatal pneumonitis (297/1694 cases)		Non-fatal pneumonitis (1397/1694 cases)		p-value
	n (%)	Available data	n (%)	Available data	
Concurrent conditions					
Respiratory failure	78 (26.3%)	297/297 (100%)	139 (10%)	1397/1397 (100%)	<0.0001
Malignant progression	66 (22.2%)		97 (6.9%)		<0.0001
Infection/sepsis	42 (14.1%)		101 (7.2%)		<0.0001
Thromboembolism	27 (9.1%)		45 (3.2%)		<0.0001
Hepatic injury	11 (3.7%)		26 (1.9%)		NS
Cardiovascular failure	10 (3.4%)		14 (1%)		0.002
Haemorrhage	10 (3.4%)		17 (1.2%)		0.007
Renal injury	10 (3.4%)		17 (1.2%)		0.007
Concurrent irAEs					
Colitis	24 (8.1%)	297/297 (100%)	90 (6.4%)	1397/1397 (100%)	NS
Haematotoxicity	22 (7.4%)		34 (2.4%)		<0.0001
Dermatitis	20 (6.7%)		85 (6.1%)		NS
Hepatitis	13 (4.4%)		37 (2.7%)		NS
Arrhythmias	11 (3.7%)		28 (2%)		NS
Thyroiditis	9 (3%)		51 (3.7%)		NS
Arthritis	6 (2%)		33 (2.4%)		NS
Diabetes	6 (2%)		15 (1.1%)		NS
Myositis	6 (2%)		16 (1.2%)		NS
Myocarditis	5 (1.7%)		4 (0.3%)		NS
Stomatitis, sinusitis and nasopharyngitis	5 (1.7%)		11 (0.8%)		NS
Nephritis	3 (1%)		16 (1.2%)		NS
Peripheral neuropathy	3 (1%)		11 (0.8%)		NS
Adrenalitis	2 (0.7%)		10 (0.7%)		NS
Encephalitis and myelitis	2 (0.7%)		6 (0.4%)		NS
Vasculitis	2 (0.7%)		3 (0.2%)		NS
Cholangitis	1 (0.3%)		7 (0.5%)		NS
Hypophysitis	1 (0.3%)		28 (2%)		NS
Meningitis	1 (0.3%)		1 (0.1%)		NS
Pericarditis	1 (0.3%)		6 (0.4%)		NS

Data are presented as n (%) or median [interquartile range] (range), unless otherwise stated. CTLA-4: cytotoxic T cell lymphocyte-associated protein-4; irAE: immune-related adverse events; PD-1/PD-L1: programmed cell-death protein-1/and its ligand.

not capture the number of individuals exposed to a given drug. Second, incomplete data in some cases precludes precise characterisation of demographics, clinical features and concomitant medical conditions that would be relevant to this patient population, such as radiation exposure or dosage, other lung disorders (COPD, interstitial or restrictive lung disease) or smoking history. In addition, database reporting is voluntary and thus, not all data fields are included in every report and quality might be variable.

In conclusion, our study highlights the increasing incidence of ICI- pneumonitis over the past few years with earlier TTO of fatal cases, emphasising the need for clinical vigilance of monitoring for ICI-pneumonitis events.

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