Therapeutics and Clinical Risk Management

Dovepress
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ORIGINAL RESEARCH

Risk of Serious Immune-Related Adverse Events with Various PD1 and PD-L1 Inhibitors: A Single-Institution, Real-Life, Comparative Study

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Background: Immune checkpoint inhibitors (ICIs) are responsible for causing immune-related adverse events (irAEs). The frequency and severity of irAEs depend on various factors, but the role of the molecule used remains unclear. Our aim was to assess the comparative safety profile of different programmed cell death-1 inhibitors (anti-PD1) and programmed cell death ligand-1 inhibitors (anti-PD-L1) in a real-life setting.

Methods: The occurrence of severe irAEs (grade ≥3) and their characteristics were recorded for all patients treated with anti-PD1 or anti-PD-L1, alone or in combination, at our center. Potential predictive factors for the occurrence of irAEs, particularly concerning the type of molecule, were identified by statistical analysis. Factors related to overall survival were also analyzed.

Results: A total of 406 patients who received at least one dose of anti-PD1 (68.5%) or anti-PD-L1 (31.5%) were included, among which 60% had lung cancer. The overall frequency of the different ICIs was 51%, 17.5%, 14.3%, 12.8%, and 4.4% for pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab, respectively. Fifty-three (13%) patients experienced severe irAEs (grade 3 or 4). While there were no significant differences with regard to ICI categories (13.7% for anti-PD1 vs 11.7% for anti-PD-L1; $p = 0.5878$), the rates of severe irAEs were significantly different between ICIs (29.6% for nivolumab, 22.2% for avelumab, 13.8% for atezolizumab, 8.2% for pembrolizumab, and 5.8% for durvalumab; $p < 0.0001$). Multivariate analyses showed that treatments with nivolumab and low polymorphonuclear neutrophil level were significant risk factors for severe irAEs. The risk of early death was lower in patients who reported severe irAEs and the risk of cancer progression was greater with one of the least toxic molecules (atezolizumab).

Discussion: This study highlights the differences in toxicity profile of various ICIs targeting the PD1/PD-L1 axis in real-life use, as well as the identification of possible predictive biomarkers.

Keywords: immune checkpoint inhibitor, programmed cell death-1 inhibitor, programmed cell death ligand-1 inhibitor, severe immune-related adverse event, predictive factor, toxicity

Introduction

Immune checkpoint inhibitors (ICIs), and especially programmed cell death-1 (anti-PD1) and programmed cell death-ligand 1 (anti-PD-L1) inhibitors, have revolutionized the treatment of many types of cancer.[1–3] However, because of their mechanism of action which involves, via the targeting of CTLA4 and PD1/PD-L1 receptors a lifting of T lymphocytes inhibition, reactivating their anti-tumor activity, ICIs may cause immune-related adverse events (irAEs) that can occur in all organs and can potentially be life-threatening and responsible for treatment interruptions.[4–6]

Recent work based on available randomized studies has suggested that toxicity may be higher with specific immunotherapy or combination therapies[7,8] but no direct comparative trials have been carried out. In addition, data

Received: 24 May 2024
Accepted: 13 February 2025
Published: 5 March 2025

from patients with pre-existing autoimmune conditions, comorbidities, and/or advanced age are lacking as these patients are often excluded from clinical trials highlighting the great need for real-life data.[9] For some time now, our institution has implemented a care plan for patients who have received ICIs, with a dedicated medical team whose role is to identify and rapidly treat irAEs. Thus, our institution has collected a large amount of individual data.[10]

The aim of the current study was to assess the comparative safety profile of different anti-PD1 and anti-PD-L1, prescribed alone or in combination with other types of chemotherapy, targeted therapy and/or immunotherapy, in a real-life setting. The secondary objectives were to determine whether the type and location of cancer have an impact on the location of irAEs and whether predictive factors for irAEs can be identified.

Patients and Methods

Study Population

Patients followed-up at our institution (European Hospital of Marseille, France), aged ≥18-years, with malignant metastatic or non-metastatic solid tumors or hematological malignancies who started treatment with ICIs (as a single agent or in combination with chemotherapy) were included. The ICI had to be a PD1 inhibitor or a PD-L1 inhibitor and to have been administered in standard clinical practice (ie, outside a therapeutic clinical trial) from the first dose at our institution.

Ethics and Regulations

This study, based on public interest, did not involve humans, but only the reuse of already recorded data. The data accessed complied with relevant data protection and privacy regulations. In accordance with French regulations, this study required neither information nor non-opposition of the included individuals, and the study was approved by the institutional and ethical review board of the European Hospital of Marseille. This study complies with the Declaration of Helsinki.

Data Collection and Definitions

Data from patients who received ≥1 dose of ICI between January 2020 and January 2023 were collected retrospectively from the pharmacy database. Efficacy and toxicity data were extracted from electronic medical records until June 12, 2023. Therapy combining PD1 or PD-L1 immunotherapy and another immunotherapy (anti-VEGF or anti-CTLA-4), such as atezolizumab-bevacizumab and ipilimumab-nivolumab, is termed "immunotherapy/targeted therapy combination".

Cancer Characteristics, Treatments, and Outcomes

Prescription software was used to obtain key dates for ICI administration (initiation, transient interruptions, and final termination). Tumor type, location of metastatic sites when present, and number of previous anti-cancer agents were obtained from multidisciplinary meeting reports. Clinical response was assessed using RECIST criteria (Response Evaluation Criteria in Solid Tumors) version 1.1.

Biological Parameters

Baseline biological abnormalities, including complete blood count (CBC), thyroid-stimulating hormone (TSH), proteinuria, serum creatinine, liver enzymes, troponine, NT-pro-BNP, and autoantibodies routinely measured at our institution (antinuclear antibodies, anti-thyroid antibodies) were collected before ICI initiation. Normal values were defined by the laboratory in charge. Abnormal CBC was considered if at least one of the following parameters had abnormal values: hemoglobin, lymphocytes, polymorphonuclear neutrophils (PMN), monocytes, or platelet counts.

Comorbidities and Comedications

Demographic data (age, sex), comorbidities (especially pre-existing autoimmune conditions and smoking), and concomitant drugs (corticosteroids, antibiotics or proton pump inhibitors (PPIs) at the time of immunotherapy initiation) were collected. Patients were considered a former smoker if they had stopped smoking at least 3 years before the first dose of anti-PD-(L)1.

Immune-Related Adverse Events

AEs were considered to be irAEs if they had occurred after the first dose of PD1 or PD-L1 inhibitor administration and were categorized by organ/system. Data about irAE management (start date, specialists involved, corticosteroids or other drugs used, efficacy of corticosteroids if used, hospitalization due to irAEs, outcomes, and date of resolution) were also collected. Toxicity was evaluated by the study investigators according to Common Terminology Criteria for Adverse Events (CTCAE version 5.0).

Statistical Analysis

Only severe AEs (grade 3–5) including all potential irAEs were analyzed. Patient characteristics were summarized as frequencies and percentages for categorical variables and mean and standard deviation (SD), or median and interquartile range (IQR: Q1–Q3) for continuous variables.

The primary endpoint was the rate of severe AEs based on ICI used, either alone or in combination with chemotherapy or another immunotherapy. Secondary endpoints included the rate of severe AEs by cancer type and location, identification of factors associated with severe AEs, treatment efficacy, and survival outcomes. Group comparisons (ICI and type) were performed using logistic regression adjusted for unbalanced data, followed by Tukey–Kramer post-hoc tests for multiple comparisons, with corresponding p-values reported.

Univariate logistic regression analysis was conducted to identify potential factors associated with severe irAEs. Variables with a p-value <0.05 in the univariate analysis were included in a multivariate logistic regression model.

Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method. OS was defined as the time from the first dose of ICI to death from any cause. PFS was defined as the time from the first dose of ICI to disease progression or death from any cause, whichever came first. Patients alive at the last follow-up or without progression were censored for OS and PFS analyses, respectively. To evaluate the duration of ICI treatment, patients who had not discontinued immunotherapy as of June 12, 2023, the last date of data collection, were considered censored. To address immortal time bias, a 6-month landmark analysis was applied, excluding patients who experienced the outcome of interest (ie, mortality or progression) before this time point.[11] Results were presented as survival rates at various time points. Univariate Cox proportional hazards regression was used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). Multivariate Cox proportional hazards regression models were applied to identify potential prognostic factors. Bias related to competing events was addressed and excluded during patient inclusion.

All analyses were adjusted for unbalanced data by applying normalized weights based on the total population. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics at Baseline

Overall, 406 patients (70% male) who received at least one dose of anti-PD1 (n = 278, 68.5%) or anti-PD-L1 (n = 128, 31.5%) during the study period were included. Among these patients, 186 (46%) received anti-PD1 or anti-PD-L1 as monotherapy, 179 (44%) in combination with chemotherapy, and 41 (10%) in combination with another immunotherapy (nivolumab-ipilimumab (n = 6), atezolizumab-bevacizumab (n = 35)). The overall frequency of the different immunotherapies received was: 51%, 17.5%, 14.3%, 12.8%, and 4.4% for pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab, respectively. Most patients received ICIs for the first time (n = 393, 97%) and as part of first-line treatment (n = 290, 71%), while 79 (19.5%) received ICIs as second-line treatment and 37 (9.1%) as third-line or more treatment.

The baseline characteristics of the patients (before ICI initiation) are shown in Table 1. Mean (SD) age at ICI initiation was 66.9 ± 11.0 years and 24 (6%) patients had a pre-existing autoimmune disease. The majority of patients (n = 247, 60.8%) were treated for lung cancer, followed by urological cancer (n = 71, 17.4%), liver cancer (n = 38, 9.4%), head and neck cancer (n = 19, 4.7%), gastrointestinal cancer (n = 17, 4.2%), gynecological cancer (n = 8, 2%), and malignant hemopathy (n = 6, 1.5%).

Table 1 Demographic and Clinical Characteristics of the Study Population

Characteristics	All Patients (N=406)
Sex, n (%)	
Female	120 (29.6)
Male	286 (70.4)
Age at ICI initiation (years)	
Mean ± standard deviation	66.9 ± 11.0
No. of courses	
Mean ± standard deviation	11.1 ± 14.4
Current smoker, n (%)	
No	18 (4.4)
Yes	76 (18.7)
Former	138 (34.0)
Not known	174 (42.9)
Immunotherapy, n (%)	
Atezolizumab	58 (14.3)
Avelumab	18 (4.4)
Durvalumab	52 (12.8)
Nivolumab	71 (17.5)
Pembrolizumab	207 (51.0)
Combination, n (%)	
Monotherapy	186 (45.8)
Monotherapy + chemotherapy	179 (44.1)
Double immunotherapy	41 (10.1)
Type of cancer, n (%)	
Gastrointestinal	17 (4.2)
Gynecological	8 (2.0)
Hemopathic	6 (1.5)
Hepatic	38 (9.4)
Lung	247 (60.8)
Head and neck	19 (4.7)
Urological	71 (17.4)
Metastatic cancer, n (%)	333 (82.0)
Treatment line, n (%)	
1	290 (71.4)
2	79 (19.5)
3	24 (5.9)
4	10 (2.5)
5	3 (0.7)
Number of immunotherapies, n (%)	
1	393 (96.8)
2	11 (2.7)
3	2 (0.5)
Cortisone, n (%)	8 (2.0)
Proton pump inhibitor, n (%)	17 (4.2)
Previous autoimmune disease, n (%)	24 (5.9)

Comparative Evaluation of the Occurrence of Severe irAEs Depending on the ICI Administered

Fifty-three (13%) patients experienced severe immune-related toxicity: grade 3 (n = 46, 87%) and 4 (n = 7, 13%) irAEs (no grade 5). Among these 53 cases of severe toxicity, 28 (52.8%) occurred for ICI monotherapy, 14 (26.4%) for ICI +

chemotherapy, 4 (7.5%) for a combination of 2 ICI and 7 (13.2%) for a combination of an ICI with a targeted therapy (anti-VEGF) (Table S1).

In decreasing order according to the total number of courses, the proportions of severe irAEs were 29.6% for nivolumab, 22.2% for avelumab, 13.8% for atezolizumab, 8.2% for pembrolizumab, and 5.8% for durvalumab (overall p-value = 0.0003) (Table 2). Rates of severe irAEs were significantly higher for nivolumab compared to pembrolizumab and durvalumab (Tukey-Kramer adjusted p for multiple comparisons were 0.0092 and 0.0029 respectively) and for avelumab compared with durvalumab (Tukey-Kramer adjusted p = 0.0383). Anti-PD1 and anti-PD-L1 comparison established that there was no significant relationship between severe irAEs and ICI category (13.7% for anti-PD1 vs 11.7% for anti-PD-L1; p = 0.5554) (Table S2). Patients who received nivolumab in association with another immunotherapy were more likely to develop severe irAEs (ie 66.7%) than patients who received durvalumab in association with chemotherapy (ie 3.1%) or pembrolizumab with chemotherapy (ie 8.1%): Tukey-Kramer adjusted p = 0.0143 and p = 0.0473 respectively (Table S1).

Association Between the Location of Severe irAEs and Cancer Location

The distribution of irAEs according to the impacted organs was: endocrinologic/rheumatologic n = 20 (37.73%), dermatologic n = 16 (30.19%), hepatic n = 5 (9.43%), renal n = 3 (5.66%), systemic n = 3 (5.66%), pulmonary n = 2 (3.77%), digestive n = 1 (1.89%), neurological n = 1 (1.89%), and cardiac n = 1 (1.89%) (Table S3). There was no association between the location of the severe irAEs and location of cancer.

Table 2 Comparison of Toxicity According to the Molecule

	Nivolumab (N=71) PD1	Avelumab (N=18) PD-L1	Atezolizumab (N=58) PD-L1	Pembrolizumab (N=207) PD1	Durvalumab (N=52) PD-L1	Overall p value*
Primary Endpoint						
Toxicity, n (%)	21 (29.6)	4 (22.2)	8 (13.8)	17 (8.2)	3 (5.8)	0.0003
Association, n (%)						<0.0001
Monotherapy	49 (69.0)	18 (100)	16 (27.6)	83 (40.1)	20 (38.5)	
Monotherapy + chemotherapy	16 (22.5)	0	7 (12.1)	124 (59.9)	32 (61.5)	
Double immunotherapy	6 (8.5)	0	35 (60.3)	0	0	
Type of cancer, n (%)						0.0005
Gastrointestinal	12 (16.9)	0	0	5 (2.4)	0	
Gynecological	0	0	0	8 (3.9)	0	
Hemopathic	2 (2.8)	0	0	4 (1.9)	0	
Hepatic	0	0	35 (60.3)	0	3 (5.8)	
Lung	34 (47.9)	0	23 (39.7)	141 (68.1)	49 (94.2)	
Head and neck	11 (15.5)	0	0	8 (3.9)	0	
Urological	12 (16.9)	18 (100)	0	41 (19.8)	0	
Metastatic cancer, n (%)	58 (81.7)	16 (88.9)	33 (56.9)	191 (92.3)	35 (67.3)	<0.0001
Treatment line, n (%)						<0.0001
1	17 (23.9)	18 (100)	45 (77.6)	160 (77.3)	50 (96.2)	
2	36 (50.7)	0	8 (13.8)	33 (15.9)	2 (3.8)	
3	11 (15.5)	0	2 (3.5)	11 (5.3)	0	
4	7 (9.9)	0	3 (5.2)	0	0	
5	0	0	0	3 (1.5)	0	
Number of immunotherapies, n (%)						0.8839
1	65 (91.6)	18 (100)	53 (91.4)	205 (99.0)	52 (100)	
2	6 (8.4)	0	3 (5.2)	2 (1.0)	0	
3	0	0	2 (3.4)	0	0	
Cortisone, n (%)	1 (1.4)	0	0	5 (2.4)	2 (3.9)	0.9208
Proton pump inhibitor, n (%)	6 (8.5)	0	2 (3.5)	7 (3.4)	2 (3.9)	0.5516
Previous autoimmune disease, n (%)	5 (7.0)	1 (5.6)	3 (5.2)	14 (6.8)	1 (1.9)	0.6578

Note: *adjusted for unbalanced data.

Predictive Factors for the Occurrence of Severe irAEs

In the univariate analysis, several factors were found to be statistically associated with severe irAEs: sex (p = 0.0204), type of ICI (p < 0.0001), combination therapy (p < 0.0001), type of cancer (p < 0.0001), number of treatment lines (p = 0.0001), previous autoimmune disease (p = 0.0259), leucocytes level (p=0.0008), PMN levels (p < 0.0001), and platelets count (p = 0.0002). There was no significant relationship (trend) between preexisting autoimmune disease and higher severe irAE occurrence (11.3% vs 5.1%, respectively; p = 0.0733).

Multivariate analyses showed several risk factors for the development of severe irAEs. Patients who received nivolumab were 6.51-times more likely to have severe irAEs than those who received atezolizumab (OR = 6.51 [95% CI 1.65–25.65] p = 0.0074); patients with hepatic, head and neck, or urological cancers were more likely to have severe irAEs than patients with lung cancer (respective ORs 4.83 [1.37–21.83] p = 0.0405, 4.03 [1.37–11.87] p = 0.0113, and 2.82 [1.33–5.98] p = 0.0067); and patients with at least three lines of treatment were more likely to have severe irAEs than patients with only one line of treatment (OR 2.74 [1.03–7.28] p = 0.0432) (Table S4). Conversely, a normal to high level of PMNs seemed to be protective against severe irAEs compared with low levels of PMNs: respective ORs 0.13 [0.02–0.89] p = 0.378 and 0.02 [0.00–0.24] p = 0.0015 (Table S4).

Overall Survival and Progression-Free Survival

The overall mortality rates were 2.0% and 10.4% in patients with and without severe irAEs, respectively (p = 0.0009). The risk of early death was significantly lower in patients with severe irAEs: (HR = 0.15 [95% CI: 0.06–0.41] p = 0.0002), thus the probability of death in patients with severe irAEs was 6.7-times less than in those with no severe irAEs (under the assumption of hazards proportionality over time) (Figure S1 and Table S5).

Regarding PFS, the overall rates of progression were 22.6% and 23.9% in patients with and without severe irAEs, respectively. The risk of progression was not different among patients with and without severe irAEs: (HR = 0.99 [95% CI: 0.68–1.44] p = 0.9602)(under the assumption of hazards proportionality over time) (Figure S2 and Table S6). Overall progression rates were 21.6% and 25.6% in anti-PD1 and anti-PD-L1 therapy groups, respectively. The risk of progression was not different among anti-PD1 and anti-PD-L1 therapy groups: (HR = 1.17 [95% CI: 0.80–1.70] p = 0.4281) (Figure 1 and Table S7). However, the risk of progression was higher in patients who received atezolizumab (anti-PD-L1) in comparison to

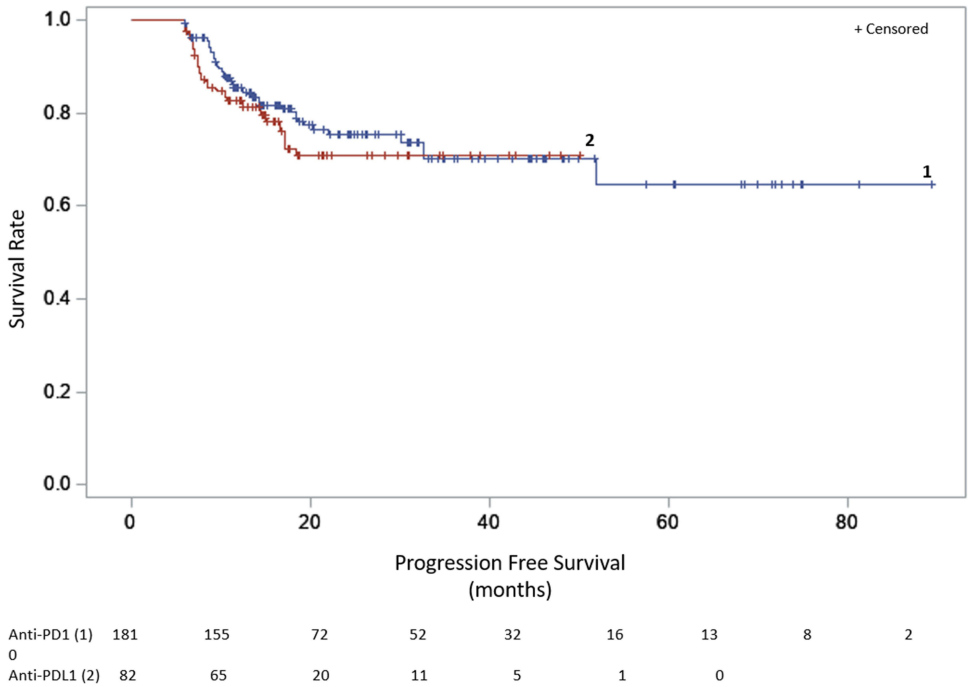

Figure 1 Kaplan-Meier progression-free survival curves according to the type of molecule: anti-PD1 (curve 1), anti-PD-L1 (curve 2): Log-Rank P=0.0064.

those who received nivolumab, or pembrolizumab (both anti-PD1): HR 2.87 [95% CI 1.22–6.78] p = 0.0160 and 3.43 [95% CI 1.74–6.73] p = 0.0004 respectively (Figure S3 and Table S8).

Discussion

This study assessed the comparative safety profile of different anti-PD1 and anti-PD-L1 ICIs in a real-life setting. The male predominance in our cohort is explained by a greater representation of lung and urological cancer compared to gynecological cancers due to the characteristics of our center. The overall rate of severe irAEs (grade ≥3) was 13.1%, which is comparable to data in the literature. Although the data from clinical trials show a prevalence of severe irAEs of around 1%, these trials only included selected patients and real-life data show rates of around 10%.[12,13] Although there was no difference in terms of severe irAE occurrence between anti-PD1 and anti-PD-L1, differences were observed when ICIs were compared individually. Significant differences in the incidence of severe irAEs (grade 3 or 4) were observed between the five ICIs prescribed to our cohort of 406 patients with various malignancies: in decreasing order: nivolumab, avelumab, pembrolizumab, durvalumab, and atezolizumab. In multivariate analysis, the risk of developing severe irAEs was 6.51-times higher in patients who received nivolumab compared to those who received atezolizumab (p = 0.0074). Although these results need to be confirmed, they add to the limited but emerging literature on the evaluation of important drugs, which have not been evaluated face-to-face in randomized controlled trials (RCTs).[7,14]

In a systematic review and meta-analysis of 36 head-to-head Phase II and III clinical trials (n = 15,370 patients), analyzing all AEs and not just irAEs, the risk of any-grade toxicity was lower with atezolizumab and nivolumab compared to ipilimumab and tremelimumab.[14] For grade ≥3 toxicities, atezolizumab and nivolumab were also safer than pembrolizumab, ipilimumab, and tremelimumab. In the lung cancer subgroup, nivolumab was safer than atezolizumab and pembrolizumab. Having immunotherapy as monotherapy was protective compared to combination with immunotherapy, immunotherapy + chemotherapy, or targeted therapy. Differences in the toxicity spectrum for each molecule were reported: atezolizumab (hypothyroidism, nausea/vomiting), nivolumab (endocrine toxicities), pembrolizumab (arthralgia, pneumonitis, and hepatic toxicities), ipilimumab (skin, gastrointestinal, and renal toxicities), and tremelimumab (rash, diarrhea, and fatigue).[14] In a network meta-analysis of 67 RCTs involving 36,422 patients, Liu et al compared the relative toxicities of ICIs and other anticancer treatments in combination or alone. Concerning ICI monotherapy, the classification of molecules according to the risk of toxicity (from highest risk to lowest risk) was as follows: tremelimumab, ipilimumab, pembrolizumab, durvalumab, atezolizumab, nivolumab, and avelumab.[7] Our results also show a better safety profile for atezolizumab, despite its frequent use with targeted therapy, but are discordant in showing an increased risk of toxicity with nivolumab. This may be due to the fact that only irAEs (and not treatment-related AEs as in Liu et al and Xu et al) were taken into account in our study, as were the use of nivolumab as second-line treatment, and potentially in combination with another ICI, which are risk factors for toxicity.[7,14] Compared to other studies in the literature, the current work analyzed a large number of ICIs and had access to high quality individual data about irAEs, avoiding the risk of over-estimation. Results in a real-life setting are important as they allow us to address this important question in less selected patients, especially those with numerous comorbidities including pre-existing autoimmune conditions, which are generally excluded from RCTs.

Concerning the secondary exploratory objectives of the current study, the overall incidence of severe irAEs (13%) was coherent with existing literature,[14,15] as was their location.[7,16] The risk of developing severe irAE was greater when the patient had received multiple lines of treatment vs first line, which is consistent with literature data showing an increased risk in the event of associated or prior radiotherapy, chemotherapy or immunotherapy.[17] The incidence of irAEs was significantly different depending on the type of cancer: lower for lung cancers, which is consistent with data from the literature, particularly from a meta-analysis of 125 clinical trials but the toxicity location did not seem to be significantly correlated with the site of the cancer (data not shown).[18] This difference in incidence according to the type of cancer may be linked to the type of molecule used and its place in the therapeutic sequence (for example, pembrolizumab rather in first line for lung cancer and nivolumab in second line), but also to characteristics specific to each cancer and its risk factors (tobacco notably).

Indeed, according to the study of Whang et al,[12] cigarette smoke and benzo(a)pyrene induce the in vivo and in vitro expression of PD-L1 on the surface of epithelial cells mediated by the aryl hydrocarbon receptor (AhR). In their study, conducted in patients with lung cancer treated with pembrolizumab, 13/16 (81.3%) patients who achieved a partial response or stable disease expressed high AhR levels, while 12/16 (75%) patients with disease progression had low levels

of AhR. In addition, PD-L1 inhibitors seemed to cause mainly liver toxicity in our cohort (p = 0.0002). Atezolizumab was mainly toxic in patients with hepatocellular cancer with 87.5% (n = 7) vs 12.5% (n = 1) in patients with lung cancer (p < 0.001). These results are similar to those of the meta-analysis of Liu et al,[7] which found the combination atezolizumab + anti-angiogenic molecule as one of the most toxic combinations compared to monotherapy. Finally, in the current study there was a low incidence of immune-induced pneumonitis, described as one of the irAEs commonly encountered in patients treated with ICIs with an incidence of up to 19%.[19] This discrepancy with the literature can be explained by the fact that this study was restricted to severe irAEs confirmed retrospectively by a trained multi-disciplinary team. Unlike the majority of other toxicities where biological and/or radiographic criteria are available to make the diagnosis, the clinical impact of immune-induced pulmonary toxicity is difficult to separate from the clinical context, mainly in patients suffering from lung cancer, and this may have led to overdiagnosis in some studies, especially those not restricted to severe grade toxicity as in the current work.

Another exploratory objective of this work was to look for potential predictive factors for severe irAEs. Statistical analysis showed that the types of ICI, the number of treatment line and the type of cancer were significantly associated with the occurrence of severe irAEs and there was a trend for presence of a pre-existing autoimmune disease. On the other hand, multivariate analysis revealed that a high PMN level could be a protective factor for developing severe irAEs. The most studied risk factors for irAEs in the literature are the presence of an autoimmune disease, presence of autoantibodies (for example anti-thyroid or antinuclear), CBC, and other generic biomarkers (high level of C-reactive protein, lactate dehydrogenase, albumin).[20] Concerning CBC, the level of PMN, and especially the neutrophil-to-lymphocyte ratio (NLR), seem to be interesting. In a systematic review on ICIs, with a meta-analysis including 6696 patients with non-small-cell lung cancer (NSCLC) from 25 studies, and in a prospective study of 1187 patients, a high NLR (>5) was identified as an independent risk factor for developing irAEs (OR = 1.04) and severe irAEs.[21,22] Conversely, other studies have shown that a low NLR was a risk factor for irAEs and the studies which analysed the absolute rate of PMN showed, as in our case, that a high PMN level was a protective factor for irAEs.[23] These encouraging results are mainly related to retrospective, heterogeneous studies on the type of cancer, irAEs, or ICI studied and must be refined. Prospective studies analysing the fluctuations in CBC during treatment could be interesting to determine whether this could be a precursor to irAEs as shown in some studies.[23–28] Interestingly, two studies[24,29] have shown that a PMN/lymphocyte ratio of ≥2.6 before initiation of ICIs in patients with NSCLC was a poor prognostic factor with significantly reduced OS and shorter PFS. These pieces of evidence showing that high PMN (or PMN/lymphocyte ratio) are associated with less irAEs and with reduced survival are in line with the association between irAEs and better PFS found in most studies including ours.[30,31] Most studies show that a low platelet count or a low platelet-to-lymphocyte ratio are risk factors for irAEs, which is in agreement with our results.[23,25,28]

Concerning overall survival and cancer progression, we found that the risk of early death was lower in patients with severe irAE, which shows on the one hand that these adverse effects generally respond well to anti-inflammatory and immunosuppressive treatments, but above all that declaring an irAE is a potential marker of good oncological response, which has been reported in several studies.[32] Interestingly, we noticed that the risk of progression was higher in patients who received atezolizumab compared to those who received other ICIs, and atezolizumab was also one of the least toxic molecules in our cohort.

Collectively, our study adds to the recent literature suggesting differences in toxicity profiles of various ICIs targeting the PD1/PD-L1 axis. More real-life data are required to validate these findings and to help clinicians better predict the risk of severe irAEs for each ICI, as well as for the type of cancer (ie, tobacco-related), and potential simple biomarkers (ie, PMN, platelet/lymphocyte or platelet/lymphocyte ratio) at ICI initiation. Such findings, if validated, could also have relevance in the context of whether to re-expose patients who have developed severe irAEs, with most recommendations proposing class changes (ie, PD1/PD-L1 instead of CTLA4) rather than intra-class changes.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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