BMC Pharmacology and Toxicology

RESEARCH

Open Access

A disproportionality analysis of real-world events from the FDA Adverse Event Reporting System (FAERS) for Atezolizumab

Zhuoyang Li[1†], Ning Zhu[2†], Yuwei Liu[1], Yan Yu[3], Tianhong Wang[4], Congcong Zou[5], Siman Wang[6] and Xiaofeng Ou[7*]

Abstract

Background An increasing number of clinical studies have highlighted the use of atezolizumab in tumor immunotherapy. However, There is still a lack of comprehensive research on its associated adverse events (AEs). To improve our understanding of its toxicological profile and to provide valuable clinical insights regarding into the effectiveness of immunotherapy, this study utilized data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) to conduct a retrospective analysis of AEs linked to atezolizumab.

Methods We extracted the reports of AEs related to atezolizumab from the FAERS database from the first quarter of 2004 to the first quarter of 2024. We quantified them using the reporting odds ratio (ROR) and proportional reporting ratio (PRR), along with chi-square value (χ^2), and conducted systematic classification of the AE signal mining results through SAS 9.4 software.

Results A total of 19,563 valid reports were incorporated, involving 20 distinct system organ class categories. The AEs related to atezolizumab, reported at the preferred term level, mainly encompassed anemia [ROR 2.33, 95% confidence interval (CI) lower limit 2.09, PRR 2.31, χ^2 255.977], febrile neutropenia (ROR 2.81, 95% CI lower limit 2.50, PRR 2.79, χ^2 333.586), neutrophil count decreased (ROR 2.14, 95% CI lower limit 1.89, PRR 2.13, χ^2 150.688), white blood cell count decreased (ROR 2.35, 95% CI lower limit 2.03, PRR 2.34, χ^2 136.673), sepsis (ROR 2.21, 95% CI lower limit 1.91, PRR 2.20, χ^2 117.741), alanine aminotransferase increased (ALT) (ROR 2.86, 95% CI lower limit 2.44, PRR 2.85, χ^2 180.031), and aspartate aminotransferase increased (AST) (ROR 2.79, 95% CI lower limit 2.38, PRR 2.78, χ^2 170.955).

Conclusions Apart from various degrees of hepatotoxicity, such as increased ALT and AST, the immune-related hematological toxicity of atezolizumab should also be noted. In clinical practice, healthcare providers should always be vigilant for the occurrence of such medication-related AEs and take measures to enhance the safety of clinical medication use.

Keywords Atezolizumab, FAERS, Adverse events, PD-L1, Hepatotoxicity, Myelosuppression

†Zhuoyang Li and Ning Zhu contributed equally to this work and should be considered as co-first authors.

*Correspondence:
Xiaofeng Ou
hxxiaoou@126.com

Full list of author information is available at the end of the article

Introduction

Malignant tumor is one of the crucial factors threatening human health. It is projected that there will be 2,001,140 new cancer cases and 611,720 cancer deaths in the United States in 2024 [1]. Malignant tumors have severely affected the quality of human life and are common diseases that pose a serious threat to human health. Currently, the main approaches for treating tumors encompass surgical treatment, radiotherapy, and pharmacotherapy. Pharmacotherapy includes chemotherapy, targeted therapy, and immune checkpoint inhibitor (ICI) therapy, among others. ICIs have entered medical practice and emerged as one of the significant immunotherapies. Among ICIs, the most extensively utilized targets are cytotoxic T lymphocyte-associated molecule-4, programmed cell death receptor-1 (PD-1), and programmed cell death ligand-1 (PD-L1) [2]. PD-L1 binds to its receptor on activated T cells, inhibiting anti-tumor immunity by suppressing the activation signals of T cells. Antibody-based PD-L1 inhibitors can induce durable tumor remission in patients with multiple cancers [3]. A considerable number of clinical trials have evidenced the remarkable efficacy of PD-1/PD-L1 inhibitors in the treatment of recurrent, metastatic or unresectable tumors, such as squamous cell carcinoma of the head and neck, hepatocellular carcinoma, and esophageal squamous cell carcinoma, etc. [4–6]. As a potent weapon in addressing the issue of cancer, a large number of PD-1/PD-L1 inhibitors have been marketed and put into clinical application [7].

Atezolizumab (MPDL3280A) is a humanized immunoglobulin G1 monoclonal antibody targeting PD-L1, which can prevent PD-L1 from interacting with PD-1 and B7-1 (CD80), thereby reversing the suppression of T cells [8]. Clinical trials have confirmed that atezolizumab has a remarkable effect on improving the prognosis of patients with unresectable hepatocellular carcinoma or non-small cell lung cancer [9, 10]. However, there are also research reports on the adverse events (AEs) that emerged during the treatment of patients with unresectable hepatocellular carcinoma using atezolizumab plus bevacizumab, such as proteinuria (25% at grade 1–2, 4% at grade 3–4), hypertension (16% at grade 1–2, 12% at grade 3–4), aspartate aminotransferase (AST) increased (11% at grade 1–2, 5% at grade 3–4), fatigue (15% at grade 1–2, 2% at grade 3–4), and so on [11]. While in non-small cell lung cancer patients undergoing atezolizumab treatment, the most frequent AEs encompass decreased appetite, dyspnoea, pyrexia, nausea, pneumonia, and so on [12]. Due to diverse AEs, patients are sometimes compelled to alter the medication dosage, interrupting the treatment, or withdrawing from it, thereby failing to reach the anticipated therapeutic targets [9, 10]. The safety concerns related to the use of atezolizumab have impeded its application in clinical setting. Currently, there is a dearth of comprehensive validation of all its potential AEs. Studying the toxicity and the spectrum of AEs of atezolizumab is of paramount importance for its clinical use.

The US Food and Drug Administration Adverse Event Reporting System (FAERS) database is intended to discern potential associations between medications and AEs during post-marketing medication safety surveillance. In light of the inherent limitations of clinical trials, the spontaneous reporting system has been utilized for pharmacovigilance to assess the safety of suspected AEs and has made substantial contributions to signal detection. We carried out a thorough search of FAERS in an attempt to present a comprehensive summary of the clinical AEs of atezolizumab and provide valuable clinical information for the outcomes of immunotherapy, while also offering personalized treatment plans for patients.

Methods

Data source

Data mining uses the original data from the FAERS database on the FDA website, which has been publicly available since the first quarter of 2004. The data is updated and released quarterly, and the study downloaded the original ASCII data package for data mining and statistical analysis. Since the database collects data through voluntary reporting, there are some duplicate reports or reports that have been withdrawn/deleted in the database; therefore, the official guidance document of the FDA provides rules for data deduplication and a list of reports to be deleted. This study strictly follows the official guidance document on the FDA website for data cleaning. The data cleaning rules are as follows: First, duplicate reports are removed according to the recommended method by the FDA, using the DEMO table's PRIMARYID, CASEID, and FDA_DT fields. The reports are sorted by CASEID, FDA_DT, and PRIMARYID, and reports with the same CASEID are retained with the largest FDA_DT value; if there are reports with the same CASEID and FDA_DT, those with the largest PRIMARYID value are retained. Second, starting from the first quarter of 2019, each data package includes a deletion report list, and after initial deduplication, any duplicate reports are removed. Reports are then removed based on the CASEID in the deletion report list.

Provide the data documentation from the FAERS database for the period from the first quarter of 2004 to the first quarter of 2024, including demographic information, medication use information, reaction terms, suspected medication treatment start and end dates, patient outcomes, reporting source, indications for use, and deleted cases. Import the data into SAS 9.4 software, deduplicate it, and select the reports where the medication name is "ATEZOLIZUMAB" as the primary suspect (PS) medication. In the database, each patient (one report) will have

Table 1 The fourfold table presenting measures of disproportionality

	AEs of interest	All other events	Total
Atezolizumab	a	b	a+b
All other medications	c	d	c+d
Total	a+c	b+d	a+b+c+d

a unique PS medication. When determining the target medication population, only consider the medication that is the patient's PS medication. If the target medication is the patient's PS medication in the analysis background database, then include the patient in the target medication population. Other patients should be included in the other medication population.

The results are matched to the preferred term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA) AEs terminology set, and then mapped to the system organ class (SOC).

Categorical variables are presented in terms of frequencies and proportions, whereas continuous variables are characterized by their median, interquartile range (IQR), and total range. The classification of an AE or suspected AE as "serious" is based on various factors such as patient outcomes, including death, life-threatening situations, hospitalization, disability or permanent damage, congenital anomaly or birth defect, required interventions to prevent permanent impairment or damage, and other significant medical events. Instances of other serious AEs encompass cases like emergency room treatment for allergic bronchospasm, serious blood dyscrasias, or seizures that do not lead to hospitalization. Conversely, a "non-serious" AE refers to an AE or suspected AE where the patient outcome does not meet the criteria defined for a serious AE.

Statistical analysis

Our study adopts a design resembling that of a case-control study, known as the case/non-case approach. We focused on AEs linked to experimental medications rather than specific medical conditions. In Table 1, to detect any potential indications of an increased likelihood of AEs related to atezolizumab, we performed a disproportionality analysis utilizing the reporting odds ratio (ROR) and proportional reporting ratio (PRR) with chi-square value (χ^2) (MHRA) [13].

In our study, individuals who received atezolizumab and experienced particular AEs were identified as "cases", while all remaining patients were classified as "non-cases". As shown in Table 2, a positive signal was generated when (i) $a \geq 3$, (ii) the ROR 95% confidence interval (CI) lower limit > 1, (iii) PRR ≥ 2 and $\chi^2 \geq 4$. SAS 9.4 was used for all statistical analyses and data processing. The FDA website recommends SAS software as one of the tools for mining the FAERS database.

Results

Descriptive results

We obtained a total of 21,161,817 reports from 81 quarters ranging from the first quarter of 2004 to the first quarter of 2024 from the official website of the FDA. After eliminating 3,534,477 duplicate reports, 709,930 cases were included for analysis. Among them, there were 19,563 reports belonging to the target population where atezolizumab was the PS medication. As presented in Table 3, excluding cases with unspecified information, male patients constituted the majority (53.64%), and the majority of all patients were aged 45 years or older (73.33%), with an average age of 65.65 years. All cases were reported more frequently after the approval in the United States in 2016, and the majority of reporters were physicians (75.76%). Among all reporting countries,

Table 2 Calculation for ROR and MHRA

	Formula	Positive signal generation
ROR	$\mathrm{ROR} = \frac{a/c}{b/d} = \frac{ad}{bc}$	(i) $a \geq 3$; (ii) ROR 95% CI lower limit > 1.
	$\mathrm{SE}(\ln \mathrm{ROR}) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$	
	$95\%\mathrm{CI} = e^{\ln(\mathrm{ROR}) \pm 1.96\sqrt{\mathrm{SE}(\ln \mathrm{ROR})}}$	
MHRA	$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$	(i) $a \geq 3$; (ii) PRR ≥ 2; (iii) $\chi^2 \geq 4$.
	$\mathrm{SE}(\ln \mathrm{PRR}) = \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}$	
	$95\%\mathrm{CI} = e^{\ln(\mathrm{PRR}) \pm 1.96\sqrt{\mathrm{SE}(\ln \mathrm{PRR})}}$	
	$\chi^2 = \frac{(ad - bc)^2(a+b+c+d)}{(a+b)(a+c)(c+d)(b+d)}$	

Table 3 Key features of atezolizumab reports from the first quarter of 2004 to the first quarter of 2024

Indicators	Cases (%)
Overall number of patients	19,563
Gender	
Female	6,684 (34.17)
Male	10,493 (53.64)
Not Specified	2,386 (12.20)
Age	
< 18 years	19 (0.10)
18–44 years	906 (4.63)
45–64 years	5,357 (27.38)
65–74 years	5,340 (27.30)
≥ 75 years	3,649 (18.65)
Not Specified	4,292 (21.94)
Mean (SD)	65.65 (12.32)
Median (Q1, Q3)	67.00 (59.00,74.00)
Min, Max	0.00, 100.00
Reporting year	
2016	253 (1.29)
2017	801 (4.09)
2018	1,269 (6.49)
2019	1,859 (9.50)
2020	2,268 (11.59)
2021	3,440 (17.58)
2022	4,199 (21.46)
2023	4,628 (23.66)
2024	846 (4.32)
Reporters	
Consumer	1,894 (9.68)
Lawyer	4 (0.02)
Pharmacist	2,275 (11.63)
Physician	15,016 (76.76)
Other health-professional	310 (1.58)
Not Specified	64 (0.33)
Serious report	
Serious	18,580 (94.98)
Non-Serious	983 (5.02)
Outcome	
Life-Threatening	851 (4.35)
Hospitalization - Initial or Prolonged	9,063 (46.33)
Disability	257 (1.31)
Death	4,577 (23.40)
Intervention	12 (0.06)
Other	7,951 (40.64)
Onset time	
Not Specified	9,058 (46.30)
Mean (SD)	109.02 (254.34)
Median (Q1, Q3)	42.00 (13.00,126.00)
Min, Max	0.00, 18,880.0

For the patients included in the analysis who were given the specified medication, individual patient data were used for statistical description. In cases where a patient experienced multiple AEs simultaneously, only one AE was considered for counting purposes

Japan (27.89%) and the United States of America (20.91%) accounted for a considerable proportion (Fig. 1). Serious reports accounted for 94.98%. The majority of patients had an outcome of hospitalization (46.33%) or death (23.40%).

The indications and reported SOC associated with the PS medication atezolizumab are illustrated in Fig. 2. The heatmap depicts the distribution of patients using atezolizumab across different indications, leading to varying levels of SOC reporting for AEs. Notably, the majority of AE reports were associated with atezolizumab use in hepatocellular carcinoma and non-small cell lung cancer.

Positive signal values of atezolizumab

As shown in Fig. 3, the number of SOC positive signals refers to the number of PT types detected by satisfying both ROR and MHRA, and all positive signals are annotated within the Venn network diagram. A total of 20 SOCs were identified as exhibiting varying numbers of positive signals. Element nodes that remain unlabeled on either side fail to meet both the ROR and MHRA criteria.

We further analyzed the PT signal and presented the positive signals PTs with a ≥ 100 in Table 4. Arranged according to the frequency of PT, the top 10 PTs are as follows: disease progression (PT: 10061818), anaemia (PT: 10002034), febrile neutropenia (PT: 10016288), neutrophil count decreased (PT: 10029366), white blood cell count decreased (PT: 10047942), sepsis (PT: 10040047), alanine aminotransferase (ALT) increased (PT: 10001551), AST increased (PT: 10003481), ascites (PT: 10003445) and proteinuria (PT: 10037032). All the computational results were provided in the supplementary information (Additional file 1).

Onset time of events

The onset time of events is displayed in Table 1; Fig. 4. Among the 19,563 cases, 9,058 cases did not report the onset time explicitly. The average onset time was 109.02 days, with a median of 42 days (IQR 13–126 days), and the longest onset time for AEs was 18,880 days. In the cases where the onset time was reported, the majority of AEs occurred within one month after the first administration of atezolizumab (4,575 cases, 43%), 1,437 cases within two months (14%), 1,049 cases within three months (10%), 712 cases within four months (7%), 545 cases within five months (5%), 358 cases within six months (3%), 1,117 cases within one year (11%), and 712 cases beyond one year (7%).

Discussion

Atezolizumab, as one of the ICIs for treating advanced cancer, has been verified by clinical trials to have obvious effects on improving the prognosis of patients with unresectable hepatocellular carcinoma or non-small cell

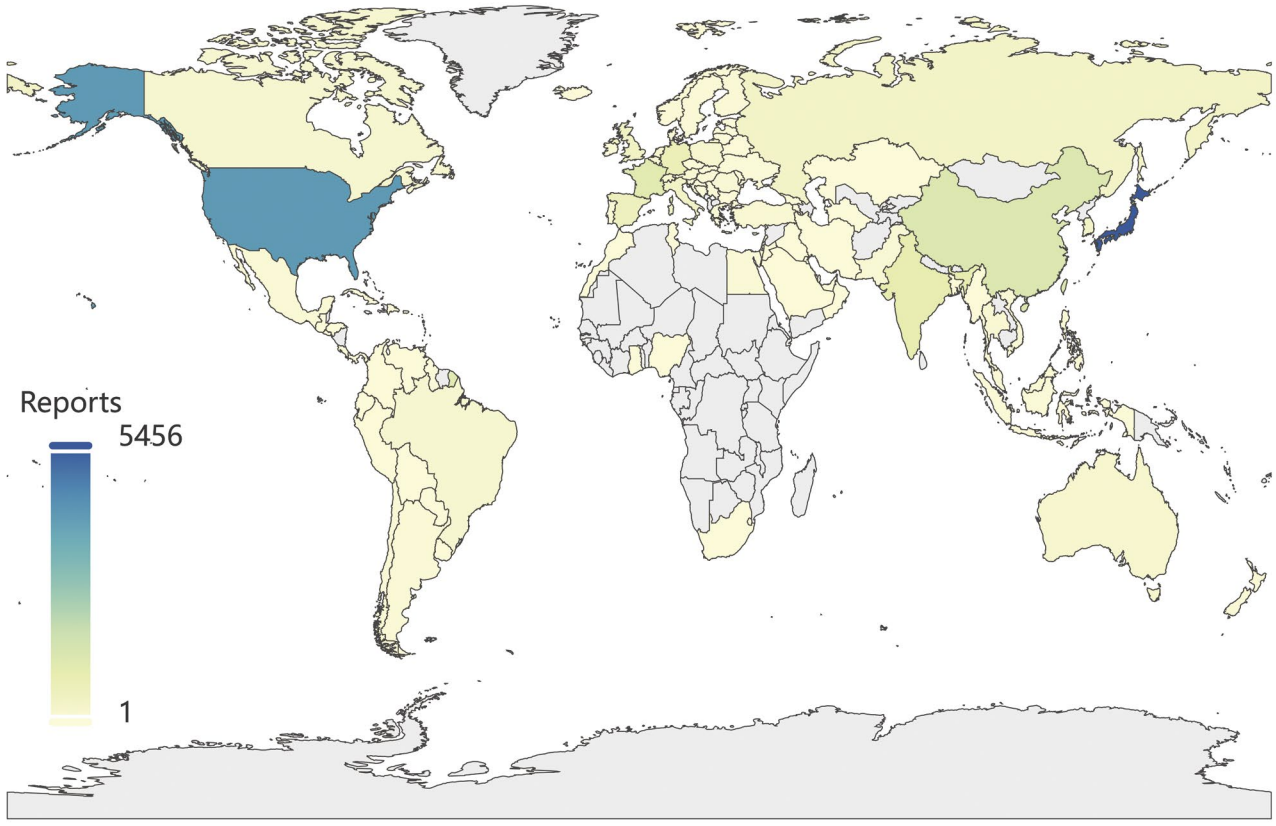

Fig. 1 Reporting countries

lung cancer [9, 10]. Given that its toxicity profile remains unclear, we conducted a data mining of atezolizumab-related AEs based on the FAERS database.

Atezolizumab-related AEs

ICIs have been associated with AEs, including liver and kidney function impairment, gastrointestinal issues, bone marrow suppression, and endocrine disturbances [14]. Atezolizumab exerts its therapeutic effect by reversing T cell inhibition [8]. However, the non-specific nature of ICIs can lead to unintended activation of immune responses against normal tissues, resulting in immune-related AEs.

In our research, atezolizumab was associated with AEs such as ALT increased and AST increased, which is consistent with the results of previous clinical trials [9, 11]. On the one hand, as an ICI for unresectable hepatocellular carcinoma, the damaging effect of the original malignant tumor on hepatocytes cannot be ruled out. On the other hand, studies have previously reported the hepatotoxicity of ICI medications, which is mainly characterized by elevated ALT and/or AST, with or without elevated bilirubin [15]. A study in 2020 summarized four possible mechanisms to account for the liver toxicity related to ICIs, encompassing direct immune toxicity, B cell involvement, the influence of the intestinal microbiota, and the depletion of regulatory T cells [16]. For cases of immune-related hepatotoxicity, it is advisable to evaluate serum transaminases, alkaline phosphatase, and bilirubin prior to each ICI treatment cycle. For patients with grade 1–2 hepatotoxicity, if symptoms do not improve within one week, glucocorticoids (0.5-1 mg/kg) should be initiated and tapered gradually over several weeks while closely monitoring the improvement of serum transaminases and bilirubin. For patients with grade 3–4 hepatotoxicity, hospitalization should be considered, and glucocorticoids at a dose of 1–2 mg/kg/day should be initiated. If there is no response to glucocorticoids within 2–3 days, alternative immunosuppressive therapies should be considered [15].

Furthermore, during the process of data mining and analysis, we also discovered AEs associated with neutrophil reduction, such as febrile neutropenia, decreased neutrophil count, and decreased white blood cell count. This might be related to the reduction of tumor-associated neutrophils (TANs) in the tumor immune microenvironment (TIME). Xue et al. demonstrated in a large-scale experiment on liver tumors that in the TIME-immune suppressive myeloid (TIME-ISM), the differentiation trajectory of neutrophils proceeds from peripheral

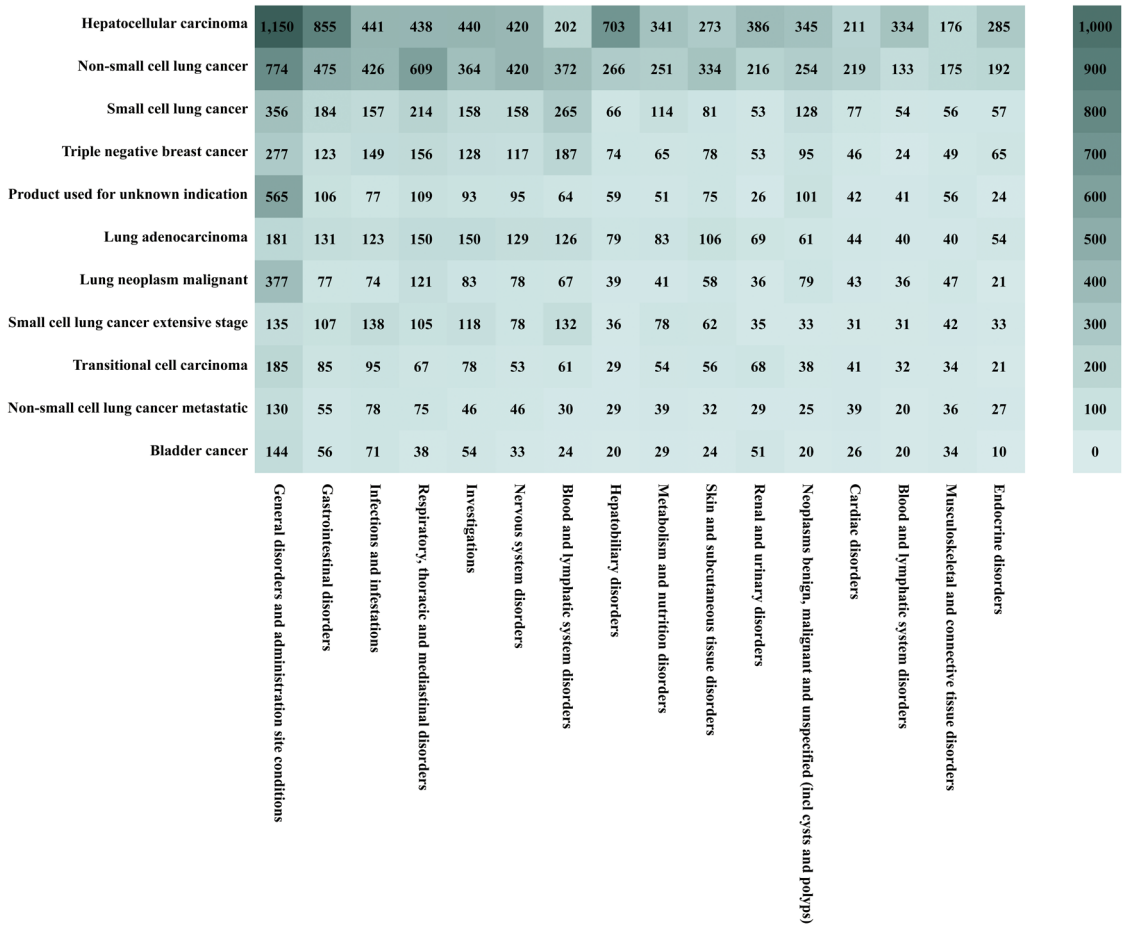

Fig. 2 Heatmap of indications and SOCs

blood neutrophils to adjacent liver neutrophils and finally to TANs, which possess pro-tumor functions. The expression of PD-L1 (CD274) on TANs is significantly higher than that on non-TANs, and PD-L1 mediates the suppressive function of TANs [17]. Atezolizumab, as a PD-L1 inhibitor, while binding to PD-L1 expressed on tumor cells, can also recognize and suppress TANs, thereby reducing the number of neutrophils. Neutrophil depletion can modify the composition of TANs, alleviate macrophage recruitment and T cell suppression, resulting in a marked decrease in the number of liver tumor nodules and tumor weight, and consequently inhibit tumor progression [17]. Immune-related hematological toxicities are relatively rare and may present in multiple manners, such as anemia, leukopenia, neutropenia, etc. In cases where immune-related hematological toxicity is suspected, it is suggested that hematologists intervene early while discontinuing ICI treatment, and the threshold for obtaining bone marrow aspiration and biopsy should be relatively low. Blood products and growth factor support, as well as intravenous methylprednisolone at a dose of 1 mg/kg, should be utilized as first-line treatments [15].

In a retrospective analysis, it was reported that in patients treated with atezolizumab and bevacizumab for advanced hepatocellular carcinoma, the risk of developing ascites increased [18]. In our analysis, ascites was also identified as one of the AEs related to atezolizumab. The study by Abiko et al. suggests that the expression of PD-L1 in tumor cells can facilitate peritoneal dissemination by suppressing the function of cytotoxic T lymphocytes, and PD-L1-targeted therapy is a strategy for preventing and treating peritoneal dissemination [19]. Another study indicated that malignant effusion can create an immunosuppressive environment leading to dysfunction of CAR-T cells [20]. The formation of ascites may not be an AE resulting from the use of atezolizumab, but rather a mechanism by which tumor cells defend against the attack of ICIs.

Furthermore, we discovered that a small number of cases had vascular disorders such as embolism. In a recent retrospective study, it was found that the addition of ICI to platinum-based combination therapy was

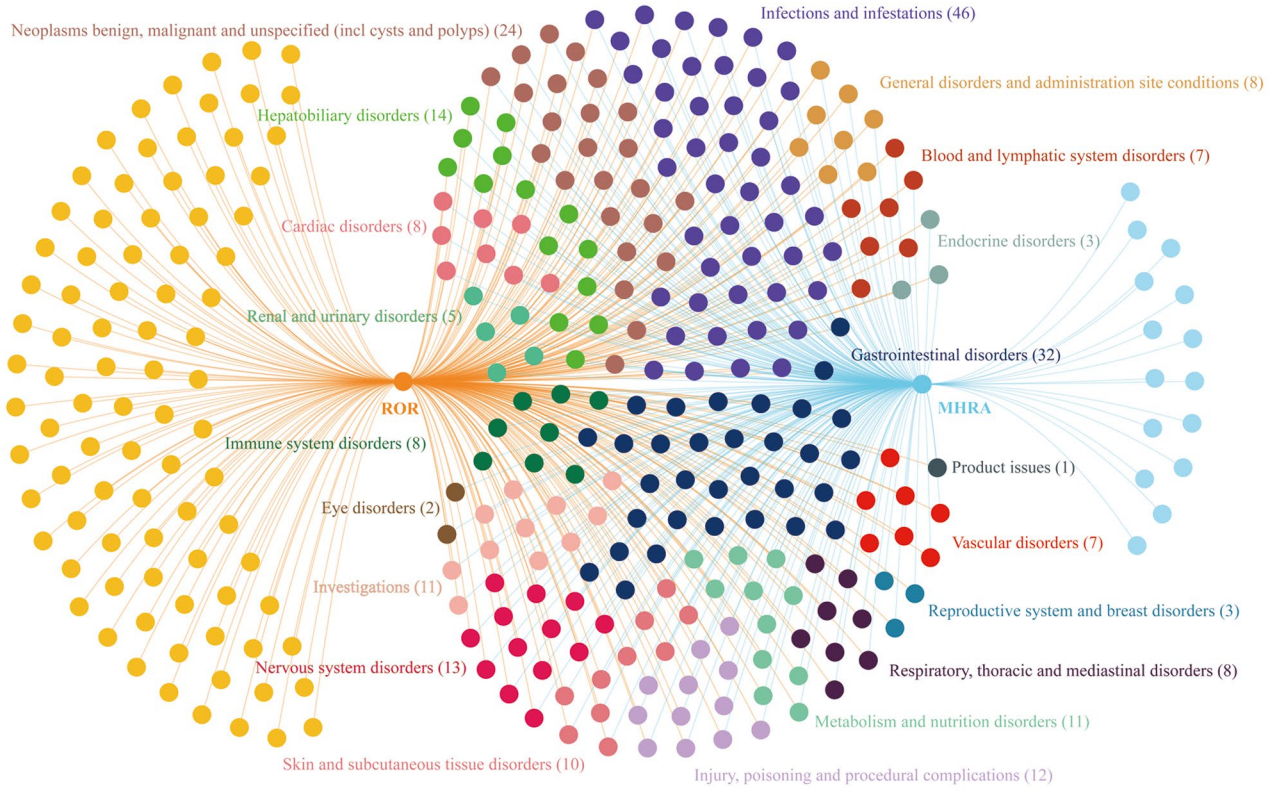

Fig. 3 AEs signal strength of atezolizumab at the level of SOC

associated with an increased risk of venous thromboembolism, whereas earlier studies considered this risk comparable [21]. This discrepancy might be related to the population included in the study [22]. Although there were not many related reports in previous studies, this AE still deserves attention in clinical practice.

Comparing atezolizumab with other ICIs

For checkpoint inhibitor-related medications, common AEs are frequently observed; however, the toxicity profiles may vary depending on the specific medication. Atezolizumab is associated with a slightly higher risk of anemia and neutropenia. Durvalumab, when used for consolidation therapy in stage III lung cancer, carries a higher risk of radiation-induced pneumonitis [23]. Avelumab, utilized for Merkel cell carcinoma, results in a marginally increased risk of skin infections linked to the tumor microenvironment [24]. Additionally, high-dose pembrolizumab treatment for DNA mismatch repair-deficient tumors with high microsatellite instability raises concerns about the risk of intestinal perforation [25].

Furthermore, the assessment of the efficacy and safety of each ICI remains inconclusive. In a retrospective observational study, Burgos-San Jose et al. evaluated three PD-1/PD-L1 inhibitors—atezolizumab, nivolumab, and pembrolizumab—for the treatment of metastatic non-small cell lung cancer. Their findings indicated that atezolizumab exhibited a balanced efficacy and safety profile compared to pembrolizumab and nivolumab [26]. However, in a study comparing ICIs, atezolizumab was found to have a higher incidence of serious AEs compared to nivolumab, durvalumab, and pembrolizumab, and exhibited only a marginally lower rate of serious AEs than ipilimumab [27]. These conflicting conclusions necessitate further detailed randomized controlled trials to rigorously assess the efficacy and safety profile of ICIs.

Limitations

Owing to the characteristics of the FAERS database itself, our research has certain limitations. Firstly, the AEs reported in the FAERS database cannot be definitely attributed to the corresponding medication. When submitting reports, the FDA does not require evidence of a causal relationship between AEs and medications, and the reports typically do not include detailed information necessary for assessing AEs. Secondly, the FAERS database is a spontaneous reporting system. Spontaneous reporting is not restricted to medical professionals; consumers can also submit reports related to AEs. And the FDA is unable to collect all reports on AEs or medication errors associated with a particular medication. The reporting of AEs or medication error incidents is influenced by multiple

Table 4 AEs signal strength of atezolizumab at the level of PT

SOC and PT	a	ROR 95% CI	PRR	χ^2
General disorders and administration site conditions				
Disease progression	994	9.91 8.71–11.27	9.72	1,834.787
Gastrointestinal disorders				
Ascites	273	4.20 3.50–5.05	4.19	275.612
Pancreatitis	119	2.03 1.60–2.56	2.02	36.671
Investigations				
Neutrophil count decreased	429	2.14 1.89–2.42	2.13	150.688
White blood cell count decreased	316	2.35 2.03–2.73	2.34	136.673
Alanine aminotransferase increased	293	2.86 2.44–3.36	2.85	180.031
Aspartate aminotransferase increased	289	2.79 2.38–3.28	2.78	170.955
Blood bilirubin increased	161	3.81 3.02–4.81	3.80	146.075
Lymphocyte count decreased	149	10.10 7.21–14.14	10.07	277.843
Respiratory, thoracic and mediastinal disorders				
Hypoxia	117	2.39 1.87–3.04	2.38	52.228
Infections and infestations				
Sepsis	311	2.21 1.91–2.56	2.20	117.741
Urinary tract infection	226	2.43 2.04–2.90	2.43	104.660
COVID-19	185	2.21 1.83–2.68	2.21	70.457
Encephalitis	148	2.76 2.20–3.45	2.75	85.835
Nervous system disorders				
Encephalopathy	112	3.71 2.81–4.89	3.70	98.481
Hepatic encephalopathy	101	10.03 6.67–15.08	10.01	187.782
Blood and lymphatic system disorders				
Anaemia	608	2.33 2.09–2.59	2.31	255.977
Febrile neutropenia	561	2.81 2.50–3.15	2.79	333.586
Hepatobiliary disorders				
Hepatic failure	182	3.12 2.53–3.84	3.11	127.658
Skin and subcutaneous tissue disorders				
Alopecia	122	2.09 1.66–2.63	2.09	40.576
Metabolism and nutrition disorders				
Hyponatraemia	248	2.48 2.10–2.94	2.48	119.346
Hypokalaemia	156	2.80 2.25–3.49	2.80	92.870
Hyperkalaemia	102	2.89 2.20–3.80	2.89	63.985

Table 4 (continued)

SOC and PT	a	ROR 95% CI	PRR	χ^2
Injury, poisoning and procedural complications				
Intentional product use issue	240	71.73 38.10-135.05	71.38	667.068
Infusion related reaction	169	2.91 2.36–3.60	2.91	107.021
Renal and urinary disorders				
Proteinuria	269	2.86 2.42–3.38	2.85	165.181
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Hepatocellular carcinoma	103	51.17 22.46-116.54	51.06	278.412
Vascular disorders				
Embolism	100	6.21 4.40–8.76	6.20	141.440

Only PTs that concurrently satisfied both algorithms and have a ≥ 100 were included. The criteria for positive signal generation were as follows: (i) a ≥ 3; (ii) ROR 95% CI lower limit > 1; (iii) PRR ≥ 2; (iv) $\chi^2 \geq 4$

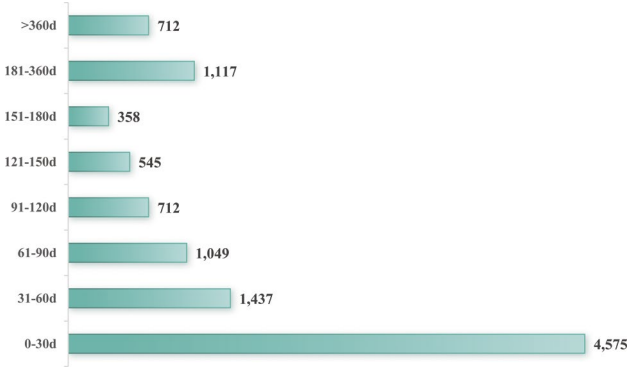

Fig. 4 Time to onset of atezolizumab-related AEs

factors. Furthermore, This study concentrated on AEs associated with single-agent therapies. To maintain clear research objectives, the investigation of combination therapies and the analysis of AE patterns specific to particular diseases were excluded from this study.

Conclusion

This study utilized the ROR and MHRA methods to mine and analyze the FAERS database, where it was found that AEs related to atezolizumab included, but were not limited to, ALT increased, AST increased, anemia, febrile neutropenia, neutrophil count decreased, white blood cell count decreased, sepsis, and ascites. In clinical practice, healthcare providers should always be vigilant for the occurrence of such medication-related AEs and take measures to enhance the safety of clinical medication use.

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase increased
AST	Aspartate aminotransferase increased
CI	Confidence interval
FAERS	The US Food and Drug Administration Adverse Event Reporting System
ICI	Immune checkpoint inhibitor
IQR	Interquartile range
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Proportional reporting ratio with chi-square value
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death ligand-1
PRR	Proportional reporting ratio
PS	Primary suspect
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
ROR	Reporting odds ratio
SD	Standard deviation
SOC	System organ class
χ^2	Chi-square

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00879-2 .

Supplementary material 1: Additional file 1.xls: The number of PT signals in SOC. A complete display of the results obtained by calculating with both algorithms.

Acknowledgements

Not applicable.

Author contributions

All authors contributed to the study conception and design. Writing—original draft preparation: [Zhuoyang Li]; Writing—review and editing: [Zhuoyang Li and Ning Zhu]; Conceptualization: [Yuwei Liu, Yan Yu, and Tianhong Wang]; Methodology: [Congcong Zou and Siman Wang]; Formal analysis and investigation: [Zhuoyang Li and Xiaofeng Ou]; Resources: [Xiaofeng Ou], and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

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

Data availability

The dataset used in this study can be accessed in the supplementary section (Additional file 1).

Declarations

Ethics approval and consent to participate

Institutional review board approval was deemed unnecessary for this study, as the FAERS database is a publicly accessible and anonymized resource (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]School of Medicine, Wuhan University of Science and Technology, Wuhan 430065, China
[2]Division of Head & Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University/West China School of Nursing, Sichuan University, Chengdu, Sichuan Province, China
[3]West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, China
[4]The Department of Clinical Research, West China Hospital, Sichuan University, Chengdu 610041, China
[5]Anesthesia and Surgery Center of West China Xiamen Hospital, Sichuan University, 699 Jinyuan West Road, Xingbin Street, Jimei District, Xiamen, Fujian Province, China
[6]Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu 610041, China
[7]Department of Critical Care Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China

Received: 2 October 2024 / Accepted: 21 February 2025
Published online: 04 March 2025

References

1. Siegel RL, Giaquinto AN, Jemal A, Cancer statistics, 2024. CA Cancer J Clin. 2024 Jan-Feb;74(1):12–49. https://doi.org/10.3322/caac.21820
2. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: Understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020;17(8):807–21. https://doi.org/10.1038/s41423-020-0488-6.
3. Sun C, Mezzadra R, Schumacher TN. Regulation and function of the PD-L1 checkpoint. Immunity. 2018;48(3):434–52. https://doi.org/10.1016/j.immuni.2018.03.014.
4. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G Jr., et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394(10212):1915–28. https://doi.org/10.1016/S0140-6736(19)32591-7.
5. Qin S, Chan SL, Gu S, Bai Y, Ren Z, Lin X, et al. Camrelizumab plus Rivoceranib versus Sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. Lancet. 2023;402(10408):1133–46. https://doi.org/10.1016/S0140-6736(23)00961-3.
6. Shen L, Kato K, Kim SB, Ajani JA, Zhao K, He Z, et al. Tislelizumab versus chemotherapy as Second-Line treatment for advanced or metastatic esophageal squamous cell carcinoma (RATIONALE-302): a randomized phase III study. J Clin Oncol. 2022;40(26):3065–76. https://doi.org/10.1200/JCO.21.01926.
7. Yi M, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 Blockade: current advances and future directions. Mol Cancer. 2022;21(1):28. https://doi.org/10.1186/s12943-021-01489-2.
8. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515(7528):563–7. https://doi.org/10.1038/nature14011.
9. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–905. https://doi.org/10.1056/NEJMoa1915745.
10. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–65. https://doi.org/10.1016/S0140-6736(16)32517-X.
11. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76(4):862–73. https://doi.org/10.1016/j.jhep.2021.11.030.
12. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387(10030):1837–46. https://doi.org/10.1016/S0140-6736(16)00587-0.
13. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci. 2013;10(7):796–803. https://doi.org/10.7150/ijms.6048.
14. Xu C, Chen YP, Du XJ, Liu JQ, Huang CL, Chen L, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ. 2018;363:k4226. https://doi.org/10.1136/bmj.k4226.
15. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(12):1217–38. https://doi.org/10.1016/j.annonc.2022.10.001.
16. De Martin E, Michot JM, Rosmorduc O, Guettier C, Samuel D. Liver toxicity as a limiting factor to the increasing use of immune checkpoint inhibitors. JHEP Rep. 2020;2(6):100170. https://doi.org/10.1016/j.jhepr.2020.100170.
17. Xue R, Zhang Q, Cao Q, Kong R, Xiang X, Liu H, et al. Liver tumour immune microenvironment subtypes and neutrophil heterogeneity. Nature. 2022;612(7938):141–7. https://doi.org/10.1038/s41586-022-05400-x.
18. de Castro T, Jochheim LS, Bathon M, Welland S, Scheiner B, Shmanko K, et al. Atezolizumab and bevacizumab in patients with advanced hepatocellular carcinoma with impaired liver function and prior systemic therapy: a real-world experience. Ther Adv Med Oncol. 2022;14:17588359221080298. https://doi.org/10.1177/17588359221080298.
19. Abiko K, Mandai M, Hamanishi J, Yoshioka Y, Matsumura N, Baba T, et al. PD-L1 on tumor cells is induced in Ascites and promotes peritoneal dissemination of ovarian cancer through CTL dysfunction. Clin Cancer Res. 2013;19(6):1363–74. https://doi.org/10.1158/1078-0432.CCR-12-2199.
20. Ma Q, He X, Zhang B, Guo F, Ou X, Yang Q, et al. A PD-L1-targeting chimeric switch receptor enhances efficacy of CAR-T cell for pleural and peritoneal metastasis. Signal Transduct Target Ther. 2022;7(1):380. https://doi.org/10.1038/s41392-022-01198-2.
21. Moik F, Chan W-SE, Wiedemann S, Hoeller C, Tuchmann F, Aretin M-B, et al. Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. Blood. 2021;137(12):1669–78. https://doi.org/10.1182/blood.2020007878.
22. Iwai C, Jo T, Konishi T, Fujita A, Michihata N, Matsui H, et al. Thrombotic risk of platinum combination chemotherapy with and without immune checkpoint inhibitors for advanced non-small cell lung cancer: a nationwide inpatient database study. Cancer Immunol Immunother. 2023;72(11):3581–91. https://doi.org/10.1007/s00262-023-03508-1.
23. Antonia A SJ, Villegas, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III Non-Small-Cell lung Cancer. N Engl J Med. 2017;377(20):1919–29. https://doi.org/10.1056/NEJMoa1709937.
24. Schadendorf D, Nghiem P, Bhatia S, Hauschild A, Saiag P, Mahnke L, et al. Immune evasion mechanisms and immune checkpoint Inhibition in advanced Merkel cell carcinoma. Oncoimmunology. 2017;6(10):e1338237. https://doi.org/10.1080/2162402X.2017.1338237.
25. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020;38(1):1–10. https://doi.org/10.1200/JCO.19.02105.
26. Burgos-San Jose A, Colomer-Aguilar C, Martinez-Caballero D, Massuti-Sureda B. Effectiveness and safety of Atezolizumab, nivolumab and pembrolizumab in metastatic non-small cell lung cancer. Farm Hosp. 2021;45(3):121–5. https://doi.org/10.7399/fh.11509.
27. Gao R, Liang W, Chen J, Yang M, Yu X, Wang X. Comparisons of adverse events associated with immune checkpoint inhibitors in the treatment of non-small cell lung cancer: a real-world disproportionality analysis based on the FDA adverse event reporting system. BMC Cancer. 2025;25(1):216. https://doi.org/10.1186/s12885-025-13614-1.

Publisher's note