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Safety assessment of proteasome inhibitors real world adverse event analysis from the FAERS database

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Proteasome inhibitor analogs (PIs) have significantly improved the degree of remission and survival rate of patients with multiple myeloma. However, serious adverse events (AEs) have hindered their clinical application. This study analyzed the AEs reported in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database to determine the safety profile and differences for the PI drugs bortezomib, carfilzomib, and ixazomib. The reporting odds ratio (ROR) was used to detect safety signals. Significant safety signals were detected based on system-organ classification (SOC). For bortezomib, the most significant SOC signal was "blood and lymphatic system disorders" (ROR = 3.47, 95% CI 3.37–3.57), while the most significant PT signal was "enteric neuropathy" (ROR = 134.96, 95% CI 45.67-398.79). For carfilzomib, the most significant SOC signal being "blood and lymphatic system disorders" (ROR = 4.34, 95% CI 4.17–4.53), while the most significant PT signal was "light chain analysis increased" (ROR = 76.65, 95% CI 57.07-102.96). For ixazomib, the most significant SOC signal was "gastrointestinal disorders" (ROR = 2.04, 95% CI 1.96–2.12), while the most significant PT signal was "light chain analysis increased" (ROR = 67.15, 95% CI 45.36–99.42). For bortezomib and carfilzomib, the top 20 reported PTs were consistent with AEs listed in the drug information. For ixazomib, six unexpected AEs were observed: asthenia, malaise, pyrexia, decreased appetite, dehydration, and falls. The PIs were consistent with the early failure model based on time-series analysis of the occurrence of adverse reactions to the drug. The data mined from FAERS generates new AE signals, and further clinical studies are needed to validate these findings.

Keywords FAERS, PIs, Multiple myeloma, Real-world study, Adverse drug events

Multiple myeloma (MM) is a malignant clonal plasma cell disease of the bone marrow that is the second most common hematologic malignancy in adults[1]. The most common signs and symptoms of MM are anemia, bone pain, renal insufficiency, fatigue, hypercalcemia, infection, and weight loss[2,3]. MM is an incurable plasma B-cell malignancy with a 5-year survival rate approximately 10–30% lower than those of other hematologic cancers[4]. Traditional standard induction therapy for MM includes a combination of corticosteroids, adriamycin, prednisone or vincristine, doxorubicin, and dexamethasone. However, the median overall survival (mOS) of patients with MM is not optimistic because of the increase in drug resistance and drug-related adverse events (AEs) associated with classical chemotherapy and glucocorticoids. In the last two decades, with the advent of new therapies such as proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and monoclonal antibodies, the prognosis of MM has improved dramatically, with OS prolonged from 3 years to 5–10 years[5].

Currently, the three most commonly used PIs are bortezomib (BTZ), carfilzomib (CFZ), and ixazomib (IXZ), which promote apoptosis by inhibiting the NF-kB signaling pathway, up-regulating NOXA (a pro-apoptotic member of the BCL-2 family of proteins), or irreversibly binding to the proteasome, leading to up-regulation of apoptosis in the MM cell line[4,6]. According to the 2024 NCCN guideline recommendations, a three-drug combination regimen based on PIs is recommended for patients with newly diagnosed MM, as well as for patients with the relapsed form of the disease. BTZ is based on the dipeptide boric acid, which reversibly inhibits the activity of the 26 S proteasome, reduces intracellular protein degradation, induces endoplasmic

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reticulum stress and apoptosis, and disrupts the cell cycle, thereby exerting antitumor effects[7]. Clinical practice and research have found that BTZ may cause serious adverse events, including nausea, diarrhea, cyclic reversible thrombocytopenia, fatigue, and peripheral neuropathy (PN). IXZ, the first oral PI, shares the same boronate-like structure as BTZ and exerts antimyeloma effects by reversibly inhibiting the proteasome β5/β1 active subunit. Owing to the structural similarity to BTZ, the adverse effects of IXZ are similar to those of BTZ, but with lesser incidence of PN. Major hematologic adverse reactions include neutropenia, thrombocytopenia, and anemia, while non-hematologic adverse reactions are dominated by gastrointestinal reactions and rash, including diarrhea, constipation, nausea, and vomiting[8]. The next-generation PI CFZ is a unique tetrapeptide epoxide ketone structure that highly selectively covalently binds to a key threonine in the β5 subunit of the proteasome, irreversibly blocking proteasomal function without off-target effects. Common adverse reactions include fatigue, anemia, nausea, and thrombocytopenia[9]. The unique molecular structure and mechanism of action of CFZ results in sustained remission and survival benefits to patients with relapsed MM. The survival benefit is more significant at the time of the first relapse. The development of MM is an evolutionary process involving multiple genes, stages, and steps, with a high degree of heterogeneity. A variety of factors affect the prognosis of patients with MM, including host factors, tumor load, cytogenetic abnormalities, and environmental factors. PIs have clear advantages for patients with high-risk MM. Unfortunately, there is a paucity of relevant studies that directly compare the safety of these three PIs. In addition, differences in PI safety may affect treatment decisions and medication adherence.

Monitoring post-marketing adverse drug events is crucial for rational clinical use, and most PI-related adverse event data originate from clinical trials. However, clinical trials are usually limited by their size and ethical constraints, making it difficult to conduct large-scale prophylactic clinical studies to comprehensively analyze all patient types. Therefore, real-world data are required to complement or validate clinical trials and better understand the safety of PIs. Large real-world databases of AEs are the primary sources of data for fast tracking and prioritizing the review of safety evaluations of marketed drugs, such as the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), which is currently the largest publicly available pharmacovigilance database. These data are important resources for evaluating the safety and efficacy of drugs and can be used for post-marketing surveillance. To study the security of PIs, we retrospectively analyzed real-world AEs of PIs from 2004 Q1 to 2023 Q4 by mining relevant data from FAERS.

Materials and methods

Data collection and source

We downloaded all reports from the publicly available FAERS database (FDA, 2024) for 2004 Q1 through 2023 Q4. Each quarterly report contains seven datasets: patient demographics (DEMO), drug (DRUG), reaction (REAC), outcome (OUTC), source of the report, and indication for treatment, and use; the DEMO, DRUG, REAC, and OUTC datasets were used in this study and linked by identifying the primary IDs (PRIMARYID) of the FAERS reports. The System Organ Classification (SOC) is the top-level classification in the Medical Dictionary for Regulatory Activities (MedDRA). We first extracted all preferred terms (PTs) using MedDRA and filtered out the PTs that appeared more than three times in FAERS. According to the FDA recommendations, when having the same PRIMARYID, we chose the most recent FDA_DT as the temporal identifier, and when the FDA_DT and CASEID were the same, we chose the higher PRIMARYID, thus eliminating duplicate reports from different individuals and organizations. Eligible reports for the following terms on behalf of the PIs: "bortezomib," "Velcade," "LDP341," "PS341," "carfilzomib," "Kyprolis," "PR171," "ixazomib," "Ninlaro," "MLN9708." Only reports with the drug code 'prime suspect' were collected for analysis.

Definition of adverse events

The AEs in the FAERS database were coded according to the PTs in MedDRA (version 26.1). MedDRA is multidirectional, and a PT can be linked to multiple SOCs; however, each PT is assigned to only one major SOC. The extracted AEs were associated with their corresponding SOCs using the MedDRA hierarchy. In this study, we analyzed only the major SOCs associated with PT, thus avoiding double counting. Any significant adverse event not listed on the label was defined as an unexpected adverse drug reaction. To minimize errors due to indications (the indication for the drug was misreported as an AE), we removed the PTs associated with indications and complications from MM and analyzed them. We only analyzed drug-induced AEs.

Data mining and analysis

We used the reporting odds ratio (ROR) algorithms for AE signal detection[10,11]. The parameters required for these algorithms were calculated using a 2×2 columnar table (Supplementary Table S1). The specific formulas for the algorithms and signal detection criteria are listed in Supplementary Table S2. The AE signals were included in the statistical tables only if they met the algorithm criteria. Statistical analyses were performed using Microsoft Excel 2021 and R version 4.4.0 software. Graphs were created using the "ggplot2" package in R software.

Results

Descriptive analysis

During the 19-year study period from January 2004 to December 2023, FAERS received a total of 20,629,811 AE reports, including 29,395 (0.12%) for BTZ, 12,753 (0.05%) for CFZ, and 8,594 (0.03%) for IXZ (Fig. 1).

The AE-reporting characteristics of the PIs are listed in Table 1.

AEs were reported in slightly more males than in females, with a higher proportion of patients aged > 65 years. The primary reporting countries for BTZ and CFZ were the United States, France, and Japan, while the primary reporting countries for IXZ were the United States and Japan. Reports were submitted by physicians,

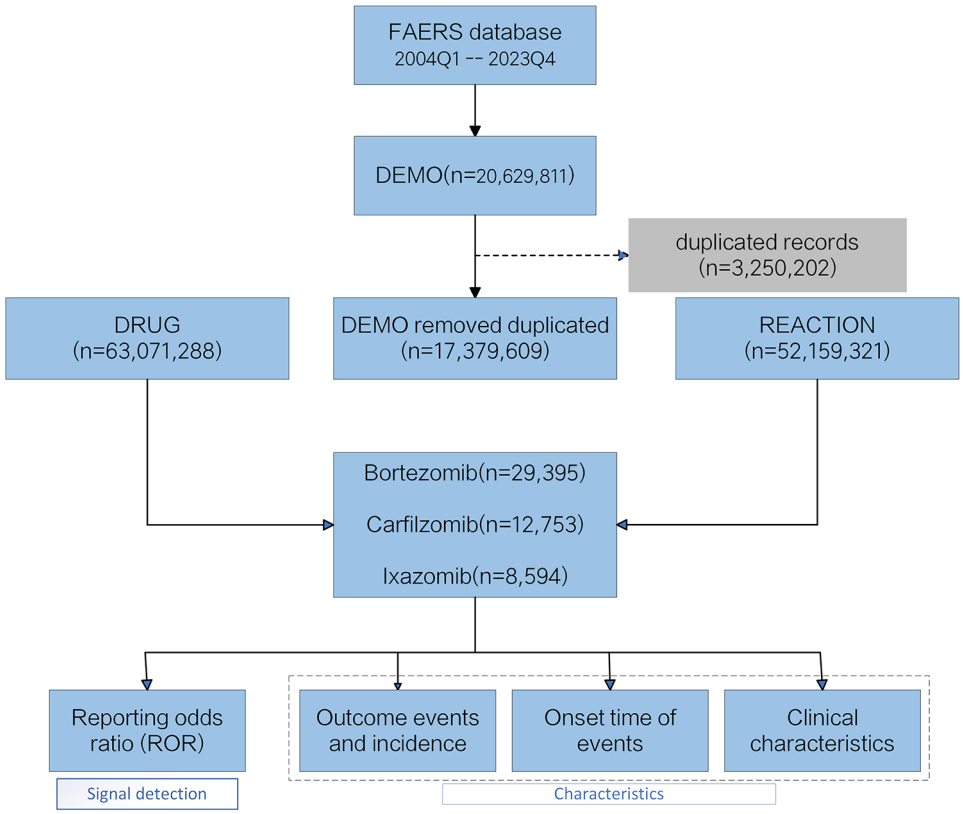

Fig. 1. Flowchart for extracting and analyzing PIs-associated AEs from FAERS database.

	Bortezomib	Carfilzomib	Ixazomib
	N^{ae} (%)	N^{ae} (%)	N^{ae} (%)
Number of adverse events reports	29,365 (100)	12,653 (100)	8596 (100)
Sex			
Female	9350 (31.8)	4498 (35.5)	4063 (47.3)
Male	12,084 (41.2)	5626 (44.5)	4075 (47.4)
Unknown	7931 (27.0)	2529 (20.0)	458 (5.3)
Age (year)			
< 18	387 (1.3)	79 (0.6)	4 (0.0)
18–65	7260 (24.7)	3788 (29.9)	1076 (12.5)
65–85	8590 (29.3)	4653 (36.8)	2729 (31.7)
≥ 85	339 (1.2)	114 (0.9)	253 (2.9)
Unknown	12,789 (43.6)	4019 (31.8)	4534 (52.7)
Reporters			
Consumer	5177 (17.6)	1314 (10.4)	2199 (25.6)
Physician	15,939 (54.3)	6934 (54.8)	3313 (38.5)
Other health-professional	3955 (13.5)	1950 (15.4)	1177 (13.7)
Pharmacist	1650 (5.6)	922 (7.3)	901 (10.5)
Others	2346 (8.0)	1422 (11.2)	870 (10.1)
Unknown	298 (1.0)	111 (0.9%)	136 (1.6)
Reporter country			
United States	10,929 (37.2)	7453 (58.9)	6831 (79.5)
France	2181 (7.5)	637 (5.0)	66 (0.8)
Japan	1255 (4.3)	617 (4.9)	1012 (11.8)
Others	15,000 (51)	3947 (31.2)	687(7.9)

Table 1. Characteristics related to proteasome inhibitors (PIs) safety reports from Q1 2004 to Q4 2023.

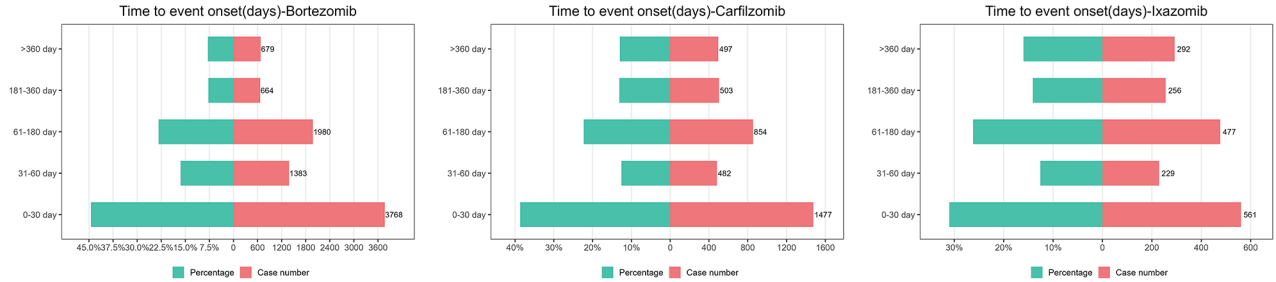

Fig. 2. Onset time of adverse reactions related to proteasome inhibitors (PIs).

	Case reports	TTO (days)		Weibull distribution				
				Scale parameter		Shape parameter		
Drugname	*n*	Median (d) (25–75%)	Min–max	α	95% CI	β	95% CI	Failure type
BTZ	8473	38	1-4043	82.64	79.73–85.55	0.64	0.63–0.65	Early failure
CFZ	3814	57	1-3653	109.53	103.90-115.15	0.65	0.64–0.67	Early failure
IXZ	2406	81	1-2406	147.24	137.22-157.26	0.71	0.69–0.74	Early failure

Table 2. Time-to-onset analysis for signals with PIs.

consumers, other health professionals, and pharmacists, with physician reports accounting for 54.3% of BTZ, 54.8% of CFZ, and 38.5% of IXZ reports.

Time-to-onset analysis and main outcomes

The time-to-onset of adverse events associated with BTZ, CFZ, and IXZ was collected from the database. Excluding associated misreporting, 8473, 3814, and 1817 AEs reported the time to onset, respectively. The median time-to-onset were 38 (interquartile range [IQR] 12–109), 57 (interquartile range [IQR] 13–190), and 81 (interquartile range [IQR] 23–222) days, respectively. As shown in Fig. 2, the results showed that most adverse reactions associated with BTZ ($n = 3768$, 44.4%), CFZ ($n = 1477$, 38.7%), and IXZ ($n = 561$, 31.0%) occurred within the first month and adverse reactions could also occur after 1 year.

However, BTZ ($n = 1980$, 23.3%), CFZ ($n = 854$, 22.3%), and IXZ ($n = 477$, 26.2%) also accounted for a larger percentage of AEs occurring after 2 months, reflecting from Fig. 2 that AEs of all three PIs may occur at any time during the year. In addition, when we fitted the time-to-onset of the three drugs to a Weibull distribution (Table 2), for BTZ, the scale parameter was 82.64 (95% confidence interval [CI] 79.73–85.55) and the shape parameter was 0.64 (95% CI 0.63–0.65); for CFZ, the scale parameter was 109.53 (95% CI 103.90-115.15), the shape parameter was 0.65 (95% CI 0.64–0.67); for IXZ, the scale parameter was 147.24 (95% CI 137.22-157.26) and the shape parameter was 0.71 (95% CI 0.69–0.74). It suggests that the risk of adverse events associated with PIs should be referred to as "early failure" and that the likelihood of adverse events decreases over time[12,13].

Nearly 50% of AE reports described serious outcomes (Fig. 3), with high rates of hospitalization (initial or prolonged) and death. BTZ had the highest proportion of deaths (15.7%) and CFZ had the highest proportion of hospitalizations (initial or prolonged; 23.7%).

Disproportionality analysis

Analysis of AEs at the SOC level

The AEs mined from the database were categorized according to the MedDRA-corresponding SOCs, involving a total of 27 SOCs. The most frequently reported SOCs for BTZ were "General disorders and administration site conditions," "Nervous system disorders," and "Infections and infestations." The most frequently reported SOCs for CFZ were "General disorders and administration site conditions," "Infections and infestations," and "Injuries, poisoning and procedural complications." The most commonly reported SOCs for IXZ were "General disorders, administration site conditions," "Gastrointestinal disorders," and "Injuries, poisoning, and procedural complications." In SOC analyses, we performed a disproportionality analysis to assess the association between AEs and organs; the larger the ROR value, the stronger the correlation. There were some differences in the SOCs associated with PIs, as shown in Table 3: BTZ had 10 significant safety signals, with the two SOCs, "Blood and lymphatic system disorders," and "Neoplasms benign, malignant and unspecified (incl cysts and polyps)," having the strongest signals (ROR > 2). CFZ had 10 significant safety signals, with "Blood and lymphatic system disorders," and "Cardiac disorders" having the two strongest SOC signals. IXZ had 7 significant safety signals, with "Gastrointestinal disorders" being the strongest.

Analysis of AEs at the PT level

Based on the decision criteria of the ROR algorithm, 850, 479, and 139 suspicious signals were identified for BTZ, CFZ, and IXZ, respectively. Supplementary Table S4 lists the 20 most frequently reported AEs. We found

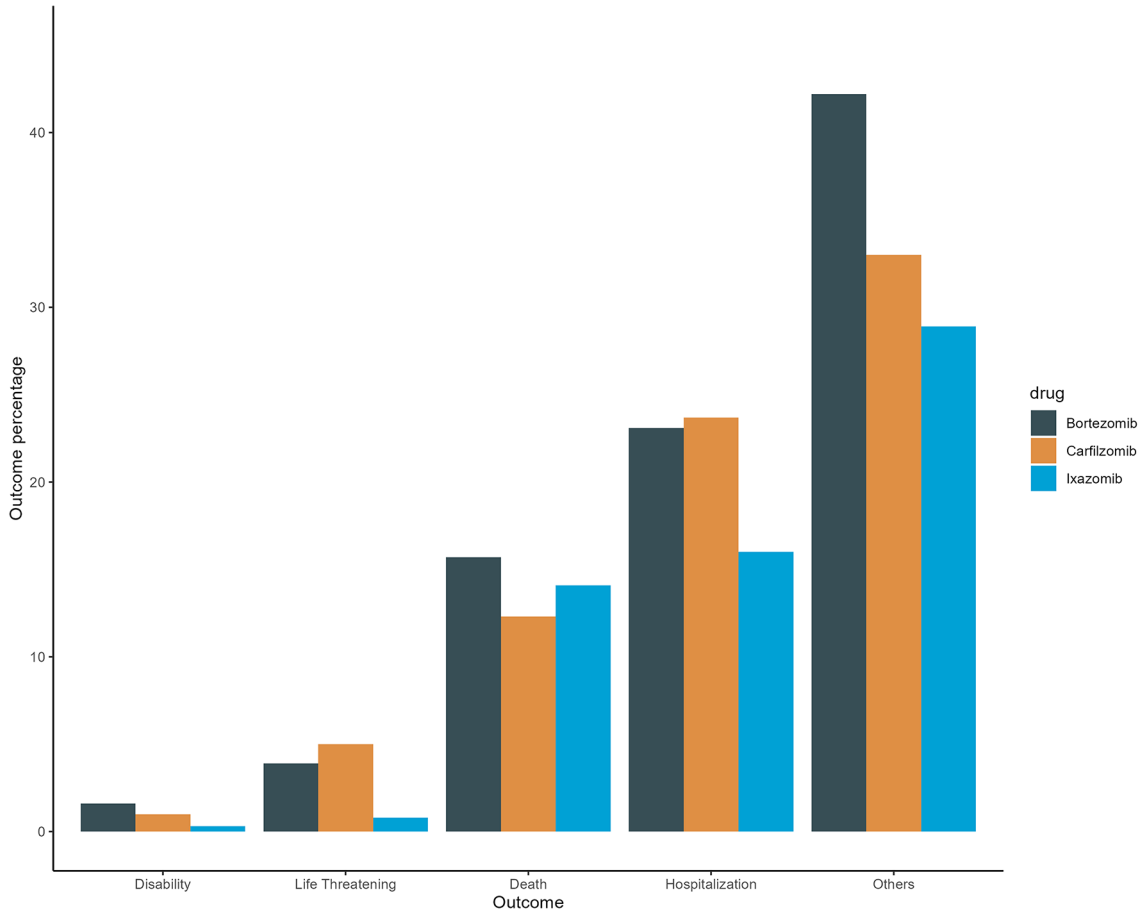

Fig. 3. Outcomes for adverse events (AEs) associated with proteasome inhibitors (PIs).

that the most common adverse reactions in BTZ were peripheral neuropathy ($n = 2,544$), diarrhea ($n = 1,470$), and pneumonia ($n = 1,207$); for CFZ, there were higher proportions of fatigue ($n = 798$), dyspnoea ($n = 608$), and pneumonia ($n = 605$); for IXZ, diarrhea ($n = 1,049$), nausea ($n = 729$), and fatigue ($n = 573$) were more prevalent. Of the reported AEs, IXZ-induced "Asthenia," "Dehydration," "Decreased Appetite," and "Fall" were not listed in the product labeling. The top 20 statistically significance PTs for each of the PIs are shown in Fig. 4.

In addition, among the PTs that conformed to the algorithm based on the ROR calculation, the forest plot (Supplementary Fig. S1) showed the top 20 PTs in terms of the strength of the three PIs. For BTZ, "Tear Break Up Time Decreased" ($n = 5$, ROR = 303.67, 95% CI 103.79-888.46), "Enteric Neuropathy" ($n = 4$, ROR = 134.96, 95% CI 45.67-398.79), and "Coombs Indirect Test Positive" ($n = 11$, ROR = 121.47, 95% CI 63.58- 232.08) ranked the strongest in terms of signal strength. For CFZ, "Panel-Reactive Antibody Increased" ($n = 3$, ROR = 602.71, 95% CI 150.73-2410.05) and "Magnesium Metabolism Disorder" ($n = 4$, ROR = 141.82, 95% CI 50.32-399.67) had the strongest signal values. For IXZ, abnormal light-chain content and blood immunoglobulin abnormalities were the PTs with the strongest reported signal values. Although these AEs are relatively underreported, the fact that these AEs are not mentioned in drug inserts indicates their value as new potential AEs.

Changes in the number of AE reports for PIs

Supplementary Figure S2 shows a line graph of the percentage of AE reports for PIs (based on the number of reports of all AEs in the class since 2004). The data are shown in Supplementary Table S5, where AEs have been recorded for BTZ since 2004. CFZ was approved for marketing by the U.S. Food and Drug Administration in the third quarter of 2012, and IXZ was approved for marketing in the U.S. in the fourth quarter of 2015. Therefore, the data for AEs in the CFZ and IXZ were only available from 2012 to 2015, respectively. Reports of BTZ-related AEs peaked in 2015 at 12.5% of all BTZ-related AEs reported over the past 19 years, then began to decline, possibly owing to the introduction of a new type of PI in the market, and began to rise slowly after 2018. In contrast, CFZ-related AEs reports peaked in 2017, followed by a rapid decline, and then a slow rise in 2020. IXZ-related AEs reports increased rapidly from the time of launch, peaked in 2019, and then declined rapidly.

Discussion

Despite structural similarities, PIs differ in their safety profiles. However, there is a lack of published studies evaluating real-world AEs after PIs are marketed. To the best of our knowledge, this is the first comprehensive

SOC	SOC code	N^{ae} (%)	ROR (95% CI)	RORL	RORU
Bortezomib					
Blood and lymphatic system disorders	10,005,329	4791	3.47	3.37	3.57
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10,029,104	6662	3.07	2.99	3.15
Infections and infestations	10,021,881	8123	1.9	1.86	1.94
Metabolism and nutrition disorders	10,027,433	2846	1.55	1.49	1.61
Cardiac disorders	10,007,541	3336	1.48	1.43	1.54
Investigations	10,022,891	6527	1.25	1.22	1.28
Nervous system disorders	10,029,205	8332	1.15	1.13	1.18
Vascular disorders	10,047,065	2112	1.15	1.09	1.2
Renal and urinary disorders	10,038,359	1893	1.15	1.1	1.2
Respiratory, thoracic and mediastinal disorders	10,038,738	4381	1.09	1.06	1.12
Carfilzomib					
Blood and lymphatic system disorders	10,005,329	2380	4.34	4.17	4.53
Cardiac disorders	10,007,541	2244	2.89	2.77	3.01
Infections and infestations	10,021,881	3560	1.98	1.91	2.05
Renal and urinary disorders	10,038,359	1025	1.53	1.44	1.63
Respiratory, thoracic and mediastinal disorders	10,038,738	2422	1.51	1.45	1.57
Metabolism and nutrition disorders	10,027,433	1044	1.44	1.35	1.53
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10,029,104	1393	1.39	1.32	1.47
Vascular disorders	10,047,065	982	1.38	1.29	1.47
Investigations	10,022,891	2596	1.28	1.23	1.33
General disorders and administration site conditions	10,018,065	6509	1.03	1	1.06
Ixazomib					
Gastrointestinal disorders	10,017,947	3234	2.04	1.96	2.12
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10,029,104	973	1.52	1.43	1.62
Blood and lymphatic system disorders	10,005,329	465	1.37	1.25	1.51
Infections and infestations	10,021,881	1488	1.34	1.27	1.41
General disorders and administration site conditions	10,018,065	4598	1.3	1.26	1.34
Investigations	10,022,891	1412	1.18	1.12	1.24
Metabolism and nutrition disorders	10,027,433	434	1.03	0.93	1.13

Table 3. Detected significant safety signals based on system organ class (SOC).

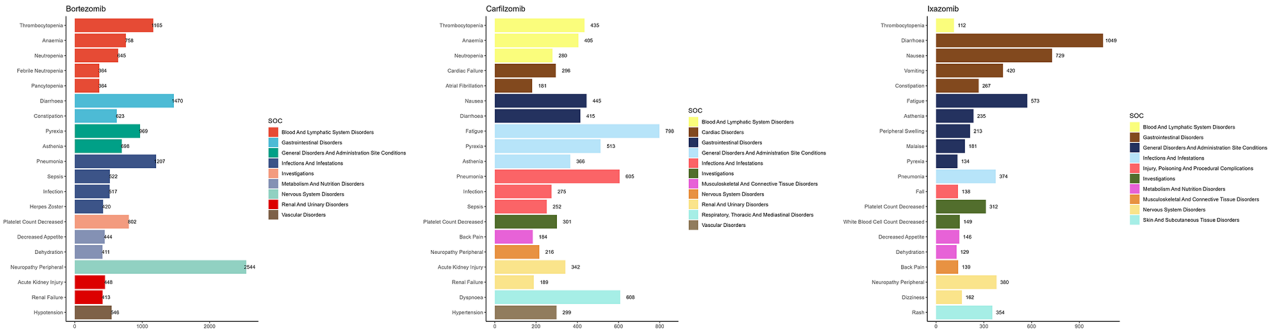

Fig. 4. Bar plot shows the statistics of the top 20 PTs of co-reported adverse events. The colour indicates the SOC of the corresponding PT. The numbers marked in the figure represent cases in which such adverse events occurred.

safety study of these three PIs using data mined from the FAERS database. In addition, we focused on the differences in the association between AEs and real-world prognoses based on the FAERS database.

Our study showed that in terms of SOC, IXZ was the only drug that showed a significant signal in "Gastrointestinal disorders." CFZ showed a significant signal in "Cardiac disorders," while BTZ was strongly associated with "Blood and lymphatic system disorders" and "Neoplasms benign, malignant and unspecified (incl cysts and polyps)." The safety of PIs in this study was consistent with previous reports on individual agents. A review study by Cengiz Seval G et al. reported that BTZ caused adverse reactions in the blood and lymphatic system[14], and Nakao et al. using a Japanese real-world database evaluated cardiac adverse events of

CFZ, which is consistent with our report[15]. Furthermore, several studies have reported serious gastrointestinal events (specifically nausea, vomiting, and diarrhea) in patients with IXZ-treated MM, which may be related to the fact that IXZ is administered orally[16–18]. The higher rates of nausea and vomiting in IXZ may also be due to the fact that its oral tablet formulation requires patients to take it on an empty stomach, which may exacerbate gastrointestinal symptoms[19].

According to our study, the most frequently reported PTs for both BTZ and CFZ, were included in the drug labeling and as warnings. PN is the most frequently reported PT in patients treated with BTZ since its marketing. A FAERS study counted PN associated with FDA-approved PIs from 1968 through June 2020, and PN is a well-known AE associated with PI treatment[20]. In patients with relapsed and/or refractory MM, single-agent BTZ resulted in PN in 35-52% of patients, with a grade 3/4 incidence of 8–14%[21–23]. It is generally consistent with our findings that BTZ predisposes to neurological disorders. A study showed that a significant inhibitory effect of BTZ on a variety of proteases, including CatG, CatA, and HtrA2/Omi was observed in vivo and ex vivo models, which inhibited neural axon growth and affected neuronal survival, and that this type of off-target effect may be related to the development of PN[24]. The prevention and treatment of PN caused by BTZ has been a hot research topic. Bortezomib enhances the S1P-S1PR1 signaling pathway in astrocytes, which leads to spinal cord neuroinflammation and PN, and the currently FDA-approved drug fingolimod prevents and reverses neuropathic pain in PN[25]. With limited strong evidence for pharmacologic treatment of BTZ-induced PN, dosage and regimen modification remains the primary treatment for PN[26,27]. Intensive neuromonitoring during BTZ therapy and the application of dose-adjustment regimens in high-risk patients can help to mitigate PN.

IXZ, the first oral PI, shares the same boronate-like structure as BTZ and exerts its antimyeloma effects by reversibly inhibiting the proteasome β5/β1 active subunit[7].

IXZ is generally well tolerated and offers a more convenient treatment for patients with relapsed and refractory multiple myeloma. However, as IXZ is similar in structure to BTZ, its use is also associated with PN development. Most BTZ-resistant PSMB5 mutant cell lines are also resistant to IXZ. Moreover, the results of our study show that adverse gastrointestinal reactions associated with IXZ included diarrhea, constipation, and nausea. In a clinical study, patients treated with IXZ experienced a longer duration of gastrointestinal symptoms, which may be due to the higher binding specificity of IXZ for the 20 S proteasome subunit[28]. The mechanisms of IXZ-induced gastrointestinal toxicity remain an ongoing area of research. Data from mouse studies suggest that pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6 are increased in intestinal epithelial cells associated with IXZ use[29]. Another proposed mechanism is dysregulation of the gut microbiome, but this has not been studied[30]. Based on our real-world studies as well as previous clinical trial studies, we recommend the use of antiemetics and antidiarrheal medications along with IXZ for coping with adverse gastrointestinal reactions. In the management of severe gastrointestinal adverse reactions, a standard approach is to interrupt PI therapy until symptoms have been effectively mitigated, followed by the resumption of treatment at a reduced dosage.

As a new generation of PIs, CFZ has a unique tetrapeptide epoxide ketone structure, which covalently binds to the key threonine of the β5 subunit of the proteasome in a highly selective manner, irreversibly blocking proteasomal function without off-target effects[31]. Therefore, the probability of PN development with CFZ use is much lower than with BTZ and IXZ use, as CFZ has a unique molecular structure and mechanism of action. CFZ can provide sustained remission and survival benefit for patients with relapsed MM, whether they are BTZ-treated or drug-resistant patients. While CFZ is associated with a low incidence of PN, AEs related to the cardiac and respiratory systems, especially dyspnoea and infectious pneumonitis, should not be neglected. Consistent with our findings, a systematic review suggests that the risk of dyspnoea occurring is higher when treated with CFZ and should be monitored more closely[32]. Our study suggests that CFZ-induced adverse cardiotoxicity is one of the PIs with a stronger signal value. [Cardiac Failure($n = 296$, ROR = 6.72, 95% CI 5.99–7.54)] A higher risk of cardiac adverse events has been reported with CFZ in Asian patients[33]. We believe that cardiotoxicity is an important cause of dyspnea. Hence, special attention should be paid to monitoring of organ functions, particularly cardiac function, when using CFZ in Asian populations. Our study showed that infectious pneumonia ranked highest in frequency of occurrence when treated with CFZ compared to the other two PIs. According to an interim analysis of a randomized phase 3 study, Pneumonia is a serious adverse event with high morbidity during CFZ treatment[34]. Therefore, the prevention of infection should be considered when administering the medication.

Notably, our study mined out adverse effects such as "Dehydration", "Fall" and "Decreased appetite" which were not mentioned in the specification and not previously reported. Among the adverse reactions reported for IXZ, "Dehydration" (ROR: 3.32, 95% CI 2.79–3.94) was a PT that was not mentioned in the drug labeling but was reported in high numbers and had a strong signal value in our analysis. In a clinical trial, serious adverse reactions to dehydration were reported in patients treated with IXZ. Mechanistically, IXZ is a selective, potent and reversible inhibitor of the 20 S proteasome, specifically inhibiting the β5 class of chymotrypsin-like protein hydrolysis sites. This inhibition may lead to an imbalance in intracellular proteostasis, which in turn affects water and electrolyte balance and may lead to dehydration and febrile symptoms[35,36]. We recommend that patients take IXZ with prompt monitoring for signs of dehydration as well as electrolyte replacement. Drinking water or diluted apple juice may be used for mild dehydration, while oral rehydration salts are required for severe dehydration. "Fall" (ROR: 1.25, 95% CI 1.06–1.48) is an AE not mentioned in previous reports and should be given serious consideration. The cause of falls could also be an AE (for example, fatigue), and this aspect requires further research. One study suggests that taking IXZ may contribute to the risk of falls, but there are no studies showing a specific mechanism of action[37]. We recommend proper medication counseling and fall risk assessment for patients taking IXZ, as well as enhanced follow-up care and monitoring. "Decreased appetite" (ROR: 1.83, 95% CI 1.55–2.15) is an adverse reaction that has never been reported, and we believe it is closely related to IXZ-induced gastrointestinal adverse reactions. Therefore, patients treated with IXZ should choose

bland foods that are easy to digest and medications if necessary. The phenomenon of intestinal obstruction after BTZ use has been repeatedly reported in previous studies, which is consistent with the results of real-world studies, where "enteric neuropathy" (ROR: 134.96, 95% CI 45.67-398.79) was the strongest signal value of the BTZ-conformant PTs reported[38,39]. Although some AE cases, such as a decrease in tear break-up time caused by BTZ, panel-reactive antibody increase caused by CFZ, and abnormal light chain analysis caused by IXZ, are relatively rare, all of them are ranked at the front of the list in terms of signal intensity. This suggests that these AEs are new and rare, but potentially significant.

The highest number of AEs was reported in our study were for BTZ, because BTZ was the first PI to be FDA approved and remains the preferred regimen for a wide range of MM treatment options in the 2023 NCCN. Interim analysis of the TOURMALINE MM3 and MM4 trials in the IXZ maintenance arm showed a possible reduction in overall survival, and 2023NCCN downgraded its recommendation to a Category 2 B regimen, leading to a reduction in its use[40]. In addition, oral dosage forms of IXZ, although more convenient to administer, are unable to overcome the adverse effects of BTZ resistance. The new generation of PIs with highly selective and irreversible action characteristics may overcome BTZ resistance, are more advantageous in terms of high-quality remission and survival benefits, have no off-target effects, lower peripheral neurological adverse effects, and have diverse regimens for combining drugs with other mechanisms of action, which may provide more optimized options for individualized treatment strategies for patients.

Data analysis using FAERS can effectively remedy the problems of smaller sample sizes, narrower coverage, and shorter observation periods in clinical trials; however, this method also has limitations. First, the majority of FAERS reports originate in the United States; therefore, the results of this study may not be generalizable due to variations in drug use and racial differences across countries[41]. Second, the FAERS database is a voluntary reporting system and there are some unavoidable problems, such as the fact that reports from ordinary consumers may not be as accurate and comprehensive as those from medical professionals, and that there may be problems of sampling bias, omission of reports, or incomplete or inaccurate reports in countries and regions with a large number of reports, thus may affect the results of our disproportionality analysis. Third, the application of the ROR calculation method for disproportionality analysis is mainly limited to generating hypotheses rather than performing hypothesis validation. Such analysis helps to identify possible drug safety alerts but does not establish a direct causal link between the drug and the adverse event. And this computational approach will inevitably lead to false positive signals (the potential inflation of type 1 error). To enhance the precision of identifying adverse events, disproportionality analyses can incorporate information from the scientific literature, clinical treatment guidelines, and official databases to enrich the database for the analysis. Despite these limitations, the FAERS database remains a unique and important tool for safety monitoring of post-marketing drugs.

Conclusion

From 2004 Q1 to 2023 Q4, we conducted a detailed review of AE safety reports submitted to the FAERS database for BTZ, CFZ, and IXZ. By analyzing 50,746 reports, we found that the most frequently reported AEs about IXZ that were not in the specification were Dehydration, Fall, and Decreased Appetite. These PIs have different safety profiles and may cause serious adverse events that may lead to treatment interruption or patient death. Clinicians should be fully aware of these safety differences in clinical care and adjust the treatment plan according to the patient's specific situation in order to improve patient adherence and reduce the occurrence of adverse events. Although some safety signals not indicated on the label have been identified in postmarketing monitoring, further prospective clinical studies are needed to validate these initial findings.

Data availability

This study is based on the FAERS database which is publicly accessible at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDEFAERS.html without requiring prior applications. Further information is available from the corresponding author upon request.

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Author contributions

J.H., P.H., and X.Z. conceived the study; J.L. and X.Y. collected the report; J.H. and M.Z. wrote the manuscript and edited the manuscript. All authors have approved publishment of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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