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A Comparative Evaluation of Adverse Effects Associated with Protein Kinase Inhibitors and Conventional Cancer Treatments

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Abstract

A comparison of the side effects associated with protein kinase inhibitors (PKIs) and other anticancer treatments was conducted using data from the FDA Adverse Events Reporting System (FAERS). The analysis encompassed 159 FDA-approved anticancer medications (71 PKIs and 88 non-PKIs) and examined 8216 distinct adverse event (AE) terms. PKIs exhibited reduced systemic toxicities overall, averaging 230.1 unique AEs per drug versus 537.7 for non-PKIs. Hematologic toxicities occurred less frequently with PKIs (e.g., febrile neutropenia: 1.93% versus 5.25%; thrombocytopenia: 2.18% versus 3.87%), along with decreased rates of infections (6.87% versus 14.2%) and immunosuppressive reactions. In contrast, gastrointestinal and dermatologic AEs were more prevalent among PKIs (such as diarrhea: 13.95% versus 8.36%). A greater share of AEs in the PKI category (14.57%) fell under the "Investigations" system organ class, compared with 9.87% in the non-PKI group. The occurrence of "Skin and subcutaneous tissue disorders" was approximately twice as high in the PKI group. Cluster analysis revealed that PKIs tended to form tighter, more uniform groups based on their AE patterns, whereas non-PKIs displayed greater diversity. Multi-kinase inhibitors targeting VEGFR were particularly associated with skin-related reactions, potentially linked to EGFR inhibition in basal keratinocytes. Although PKIs offer more precise mechanisms, drug resistance continues to pose difficulties, underscoring the importance of biomarker-guided approaches. Overall, these findings demonstrate the better tolerability of PKIs while highlighting the value of individualized treatment strategies to balance effectiveness and safety.

Keywords: Pharmacovigilance, Drug-related side effects, Target-specific safety profile, Oncology pharmacotherapy, Adverse effects, Adverse events

Introduction

Cancer cells exhibit disrupted cell cycle regulation along with other defining characteristics [1]. Protein kinases serve as key mediators in most signal transduction pathways by modulating substrate activity and regulating numerous cellular functions, such as metabolism, transcription, cell cycle advancement, cytoskeletal dynamics and motility, apoptosis, and differentiation. Phosphorylation and dephosphorylation processes are believed to affect roughly 50% of all proteins [2]. Consequently, protein kinases have attracted considerable interest over the past few decades due to their central role in signaling networks [3]. Mutations or overexpression of kinase genes contribute significantly to the onset of multiple cancer types by activating pathways that generate proteins driving oncogenesis [4].

Dysregulated kinase activity frequently drives cancer advancement, positioning protein kinases as critical targets for drug development [5]. The emergence of small-molecule kinase inhibitors (KIs) has revolutionized oncology by enabling therapies that

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selectively block these aberrant signaling routes [6]. Since their introduction more than two decades ago, protein kinase inhibitors (PKIs) have become prominent options in cancer management. Imatinib, granted FDA approval in 2001, was the first small-molecule kinase inhibitor approved for the treatment of chronic myelogenous leukemia in blast crisis [7]. PKIs primarily act on protein kinases that govern essential signaling cascades controlling cell growth, proliferation, and survival. This targeted approach distinguishes them from conventional cytotoxic chemotherapies, which broadly target proliferating cells and often cause substantial damage to healthy tissues [8]. Agents that inhibit multiple kinases simultaneously are advantageous against multifaceted cancers and help circumvent resistance that commonly arises with single-target therapies [9]. Additionally, the oral route of administration for many PKIs enhances patient adherence compared with most cytotoxic agents, which generally require intravenous delivery [10].

Nevertheless, PKIs for cancer therapy face several limitations that affect their clinical utility and outcomes. A major issue is acquired resistance in cancer cells, which may arise from kinase domain mutations that hinder drug binding, upregulation of bypass signaling pathways that maintain cell viability, or secondary mutations within the kinases [11, 12]. Complete selectivity remains challenging due to structural similarities in ATP-binding sites across the kinase family [13], which often result in unintended off-target interactions and heightened toxicity risks [14]. Pre-existing kinase mutations can also confer primary resistance before treatment initiation [12]. Furthermore, effective use requires detailed knowledge of tumor biology to predict individual responses, promoting personalized regimens that incorporate biomarkers and kinase profiling tailored to each patient's cancer characteristics [15].

PKIs employed in neoplasm treatment possess distinctive adverse event (AE) profiles shaped by their specific mechanisms and target interactions. They are frequently linked to cardiovascular toxicities including hypertension, heart failure, arrhythmias, thromboembolism, and worsening of coronary artery disease, largely through interference with kinases essential for cardiac physiology [16]. Many also cause mild liver toxicity, requiring regular monitoring of liver function markers [17]. Dermatologic reactions, such as skin rashes, are widespread in this class, with differences based on the targeted kinase [18]. Mild gastrointestinal complaints that may affect quality of life and treatment compliance are similarly noted [19].

Traditional cytotoxic chemotherapies, by contrast, non-selectively damage rapidly dividing cells by disrupting DNA synthesis or mitosis. This broad mechanism kills malignant cells but also harms normal proliferative tissues in the bone marrow, digestive lining, and hair follicles, producing widespread toxicities like myelosuppression (with consequent infections and anemia), nausea, vomiting, and alopecia [8]. Resistance to these agents commonly develops through mechanisms such as decreased cellular uptake, increased detoxification, impaired prodrug activation, enhanced DNA repair, or increased drug efflux [20].

Accordingly, the present study seeks to evaluate and contrast the safety characteristics of PKIs versus non-PKI anticancer agents by analyzing data from the FDA Adverse Events Reporting System (FAERS).

Materials and Methods

Selection of the cancer drugs

All medications categorized under the WHO ATC code L01 Antineoplastic agents were retrieved from the WHO ATC database [21]. The list was refined by excluding combination products, biologic agents, and any drugs lacking FDA approval. The resulting information was compiled into a database and classified by each inhibitor's primary target.

Preparation of AE database for approved anticancer drugs

FAERS represents a key regulatory pharmacovigilance database widely applied by the FDA and marketing authorization holders for safety signal identification. Its value lies in encompassing post-marketing data for all U.S.-approved drugs, which supports labeling updates and enables class-wide or comparative safety evaluations [22].

Adverse events in FAERS are consistently coded using the Medical Dictionary for Regulatory Activities (MedDRA) [23], the international standard for regulatory reporting of AEs and indications. MedDRA employs a five-level hierarchical structure, progressing from highly specific lowest-level terms (LLTs) to broader system organ classes (SOCs). The analysis focused on Preferred Terms (PTs)—unique descriptors for symptoms, signs, diagnoses, investigations, procedures, and histories—as

well as SOCs organized by etiology, anatomic site, or purpose [23]. LLTs include over 8000 granular terms grouped into 27 SOCs.

Data extraction from FAERS was performed via the OpenVigil interface [24], a specialized pharmacovigilance platform for detecting novel adverse reactions. OpenVigil incorporates data cleaning steps to eliminate duplicates, address missing values, standardize drug names and AE terminology, and improve overall data integrity. The tool offers a user-friendly web interface for querying, filtering, and exporting results, along with disproportionality metrics such as the Reporting Odds Ratio (ROR). ROR quantifies the relative reporting frequency of a specific AE for one drug compared with all others [25]. It represents the odds of an AE among reports involving the drug of interest, relative to the odds among reports for other drugs [26], derived by comparing event odds in cases versus non-cases [27].

OpenVigil was queried in October 2024 to retrieve AEs linked to the selected PKIs and non-PKIs, including associated descriptive statistics. The MedDRA version applied was 24.0. Agents lacking sufficient data in OpenVigil 2.0 or inadequate reports for meaningful analysis were omitted.

Only AEs meeting the criteria of ROR $\geq$ 2.0, lower limit of the 95% confidence interval > 1.0, and at least three reported cases were retained to minimize background noise and enhance analytical sensitivity [27].

Data analysis

The Kruskal–Wallis test was used to compare the two independent groups (PKI and non-PKI). Frequency values for each AE Preferred Term (PT) served as the variables for detecting statistically significant differences. A P-value of < 0.05 was considered statistically significant, and the significant mean differences were further examined.

To evaluate potential differences in the distribution patterns of PTs across the PKI and non-PKI groups, a nonparametric independent-samples median test was performed using SPSS Statistics 26.0 [28]. The null hypothesis was rejected when the p-value was less than 0.05.

Cluster analysis

To strengthen clustering reliability and reduce noise stemming from the large number of sparse entries, the dataset was pre-processed by excluding PTs reported for only seven or fewer drugs (representing less than 5% of the total anticancer drug set). This 5% cutoff represents a standard approach in high-dimensional data processing that maintains adequate coverage while reducing interference from rare adverse-event terms, thereby supporting more distinct pattern recognition. Hierarchical clustering was subsequently performed using the furthest-neighbor (complete linkage) method and Euclidean distance as the similarity measure. This combination was chosen for its capacity to produce clearly delineated clusters and effectively highlight potential outliers. All clustering procedures were executed in SPSS Statistics 26.0 [28].

Results and Discussion

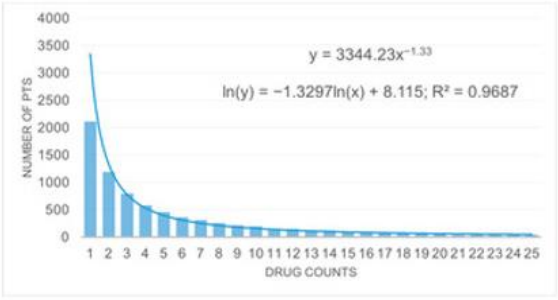
Anticancer drug dataset

The analyzed dataset (designated AC) comprised 159 FDA-approved anticancer agents classified under the ATC code L01 Antineoplastic agents. Combination therapies, monoclonal antibodies, and other biologic products were deliberately omitted to enable a more precise assessment of individual drug safety profiles. The AC dataset was partitioned into two subsets: the PKI subset, containing 71 protein kinase inhibitor agents, and the non-PKI subset, encompassing 88 molecular entities. The non-PKI subset incorporated diverse therapeutic categories based on ATC classification: 12 alkylating agents (L01A), 16 antimetabolites (L01B), 10 plant alkaloids and other natural products (L01C) with inherent cytotoxic properties, 10 cytotoxic antibiotics and related substances (L01D), and 40 additional antineoplastic agents (L01X). A complete listing of all evaluated drugs with their corresponding ATC codes appears in Section 3.4.

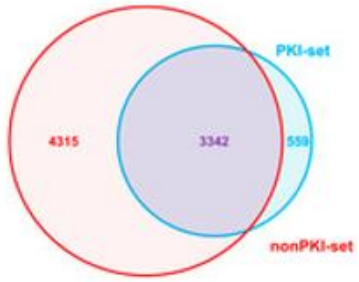
Processing the AC dataset yielded 8216 unique AE Preferred Terms (PTs). The most commonly reported PT was “disease progression,” documented for 132 drugs (82.5% of the entire set). This was followed by “malignant neoplasm progression” associated with 113 drugs (70.6%) and “thrombocytopenia” linked to 106 drugs (66.3%). Additionally, 2115 PTs were reported for only a single drug across the whole collection.

Figure 1a depicts the relationship between the number of drugs and the count of associated PTs, revealing a distinct power-law distribution. For instance, 2115 PTs were connected to just one drug, while 1188 PTs were tied to exactly two drugs. Such distributions typically feature a limited number of drugs linked to many PTs, with most

drugs associated with relatively few PTs. **Figure 1b** presents a scaled Venn diagram that details the overlap and unique distribution of AE-PTs between the PKI and non-PKI subsets.



a)



b)

Figure 1. (a) Count of PTs recorded in relation to the number of drugs associated with each observed PT; (b) Distribution showing PTs unique to the PKI set, PTs unique to the non-PKI set, and PTs common to both sets

The non-PKI set had 7657 recorded PTs, whereas the PKI set had 3901. Despite the comparable number of drugs in both groups, the PKI set displayed a markedly more limited range of PTs, reflecting greater uniformity within this category. When examining the number of unique PTs linked to individual drugs, methotrexate showed the largest count at 3240 PTs, followed by cyclophosphamide (2369 PTs), doxorubicin (1894 PTs), vincristine (1822 PTs), and carboplatin (1668 PTs). The top 20 drugs ranked by the highest number of associated PTs were all from the non-PKI group. The first PKI to appear in this ranking was imatinib, at 21st position, with 886 PTs. On average, each drug in the PKI set was linked to 230.1 distinct PTs, in contrast to an average of 537.7 PTs per drug in the non-PKI set.

For each drug in the AC dataset, the reporting frequency of all associated PTs was computed, yielding a total of 63,881 data points. The maximum frequency observed was 52.37 percent for diarrhea (corresponding to 740 event reports) with neratinib. The minimum frequency was 0.001475%, recorded for 1139 PT events with palbociclib. The mean frequency across all events in the PKI set was 0.721 percent, while the mean frequency for the non-PKI set was 0.345 percent. The overall average number of AEs across the dataset was 443. The distribution of these observed frequencies is summarized in **Table 1**.

Table 1. Number of PTs reported by the occurrence frequency range.

Range of frequency	> 10%	1%–10%	0.1%–1%	0.01%–0.1%	0.001%–0.01%
Number of AEs values	303	5733	21,426	30,101	6318

The frequency distribution revealed a strong concentration of values at the lower end of the spectrum. Around 57% of the frequencies were situated below the 0.01% mark. Just 303 data entries surpassed the 10% level, and these higher values came from 119 drugs included in the AC collection. Every drug examined displayed at least one PT with a reporting frequency of at least 1%. When looking specifically at the PTs, a total of 820 adverse events reached frequencies above 1%. Additionally, the results showed that the count of reported events grew steadily as the frequency of occurrence declined.

The number of case reports obtained for each drug varied substantially, from a low of 39 for methyl aminolevulinate (which received FDA approval in January 2022 for treating atopic dermatitis) to a high of 271,252 for methotrexate. Methotrexate holds FDA approvals for a broad range of uses across various medical fields and patient groups, such as maintenance therapy in combination regimens for acute lymphoblastic leukemia, metronomic combination treatment for relapsed or refractory non-Hodgkin lymphoma, mycosis fungoides, rheumatoid arthritis, severe psoriasis, and polyarticular juvenile idiopathic arthritis. Cyclophosphamide followed with 103,517 case reports, while celecoxib ranked third at 71,488 reports. Across the full dataset, the average number of case reports per drug was 13,280.7, and the median was 3,847.

Analysis of the PKI dataset

After applying the established selection filters, the group of 71 PKI drugs yielded 3,901 distinct Preferred Terms (PTs). The average reporting frequency for each PT was determined by aggregating data across the drugs in this subset. These mean frequencies ranged from 0.0058% to 17.69%. "Disease progression" was the most widely shared PT, appearing in reports for 62 drugs. This was succeeded by "malignant neoplasm progression" (52 drugs) and diarrhea (49 drugs). **Table 2** presents the PTs with average frequencies greater than 5%, ranked from highest to lowest, and includes the number of drugs linked to each term. Altogether, 240 unique PTs achieved an average frequency surpassing 1%

Table 2. PTs with a calculated mean value higher than 5%.

PT	Number of drugs associated with the PT	Mean of the frequencies (%)
Death	44	17.69
Diarrhea	49	13.95
Off-label use	24	11.34
Fatigue	40	10.92
Nausea	28	10.72
Extra dose administered	1	9.72
Blood glucose increased	2	9.61
Product dose omission issue	10	9.21
Rash	30	8.40
Dyspnoea	4	6.62
Headache	3	6.60
Pyrexia	24	6.47
Pain	2	6.46
Dizziness	5	6.40
Product use in unapproved indication	9	6.27
Idiopathic pulmonary fibrosis	1	6.07
Vomiting	28	6.02
Hair colour changes	6	6.02
No adverse event	8	5.78
Arthralgia	7	5.63
Pruritus	7	5.47
Vitamin B1 decreased	1	5.27
Alopecia	16	5.27

The majority of PTs appeared in reports for more than three drugs, showing a median of 8 drugs and an average of 15 drugs per PT. Only three events exhibited a mean frequency above 5% in association with a single drug. Decreased vitamin B1 levels were noted specifically for fedratinib; this represents a well-recognized and highly characteristic side effect that can progress to Wernicke encephalopathy. Idiopathic pulmonary fibrosis was documented for nintedanib, a drug also indicated for managing this condition. Pain demonstrated elevated mean frequency values with pexidartinib and fruquintinib. However, given the generic nature of this symptom, formulating a specific causal explanation remains challenging. The adverse events that displayed both elevated mean frequencies and broad occurrence across numerous drugs—such as death, diarrhea, fatigue, rash, nausea, pyrexia, and vomiting—represent common and anticipated reactions during cancer therapy.

The nonparametric independent-samples median test was conducted on the frequency distributions of all AE-PTs for drugs across the two groups, encompassing a total of 3,342 variables. Statistically significant differences emerged for only 102 PTs. Among these, 59 PTs showed lower average frequencies in the PKI group compared with the non-PKI group, while 43 PTs displayed higher average frequencies in the PKI group.

The magnitude of these differences spanned from −5.59% to +3.32%. Although most differences were relatively modest, several more pronounced exceptions were evident, especially concerning hematologic issues.

For 79 PTs, the difference ranged from −0.5% to +0.5%. The PTs demonstrating absolute differences greater than 0.5% are detailed in **Table 3**.

Table 3. Comparison of Adverse Event Frequencies between PKI and Non-PKI Drug Groups for PTs With Mean Occurrence Rates Above 0.5%

Preferred term (PT)	Average frequency in non-PKI group (%)	Average frequency in PKI group (%)	Difference between groups (%)
Febrile neutropenia	5.25	1.93	3.32
Neutropenia	5.10	2.74	2.36
Thrombocytopenia	3.87	2.18	1.69
Anemia	4.09	2.80	1.30
Myelodysplastic syndrome	1.25	0.28	0.97
Mucosal inflammation	1.87	0.90	0.97
Pancytopenia	2.13	1.26	0.87
Hepatic pain	0.81	0.10	0.71
Bone marrow failure	1.31	0.66	0.65
Hematotoxicity	0.83	0.23	0.60
Respiratory failure	1.54	0.95	0.59
Leukopenia	1.39	0.82	0.57
Abnormal hepatic function	0.78	1.36	−0.58
Increased white blood cell count	0.61	1.26	−0.65
Central nervous system metastases	0.57	1.62	−1.05
Cryptococcosis	0.05	1.11	−1.06
Metastatic breast cancer	0.87	1.97	−1.10
Reduced appetite	3.61	4.74	−1.13
Nail-related disorders	0.19	1.32	−1.13
Drug resistance	0.58	1.93	−1.35
Cognitive impairment/disorder	0.63	2.18	−1.55
Chronic myeloid leukemia	0.20	2.20	−1.99
Diarrhea	8.36	13.95	−5.59

Examination of the data shows that most PTs appearing in **Table 2** with positive difference values belong to the "Blood and lymphatic system disorders" system organ class (SOC). This pattern suggests comparatively milder bone marrow suppression with PKI agents compared with conventional cytotoxic therapies. Certain PTs, including metastases to the central nervous system, breast cancer metastasis, drug resistance, and chronic myeloid leukemia, likely correspond to indicators of disease advancement or reduced therapeutic effectiveness within the PKI group when compared to the non-PKI group. Such differences can be attributed to the selective, mechanism-based action of PKIs, which contrasts with the more indiscriminate impact of other antineoplastic treatments.

When cross-referencing the PTs in the PKI set with mean frequencies exceeding 5% (**Table 2**) and those demonstrating statistically significant differences between the two groups (**Table 3**), diarrhea emerges as the sole overlapping term. This indicates that, except for diarrhea, the other commonly reported PTs in **Table 2** did not show meaningful differences in average frequency between PKI and non-PKI drugs. The absence of significant differences for the remaining 23 PTs listed in **Table 2** may be explained by the relatively small number of drugs associated with certain terms, such as extra dose administered, blood glucose increased, dyspnoea, headache, pain, idiopathic pulmonary fibrosis, and vitamin B1 decreased.

The system organ class displaying the greatest number of notable differences between the groups was "Blood and lymphatic system disorders" (16 PTs), followed by "Gastrointestinal disorders" (15 PTs), and then both "Investigations" and "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" (9 PTs each).

Analysis based on SOC classification

All 8,216 identified AE-PTs were assigned to their respective system organ class (SOC) categories. The three SOCs containing the largest number of PTs were Investigations (914 PTs), Gastrointestinal Disorders (852 PTs), and Infections and Infestations (722 PTs). A complete overview of all SOC categories, including the count of PTs in each, is provided in **Figure 2**.

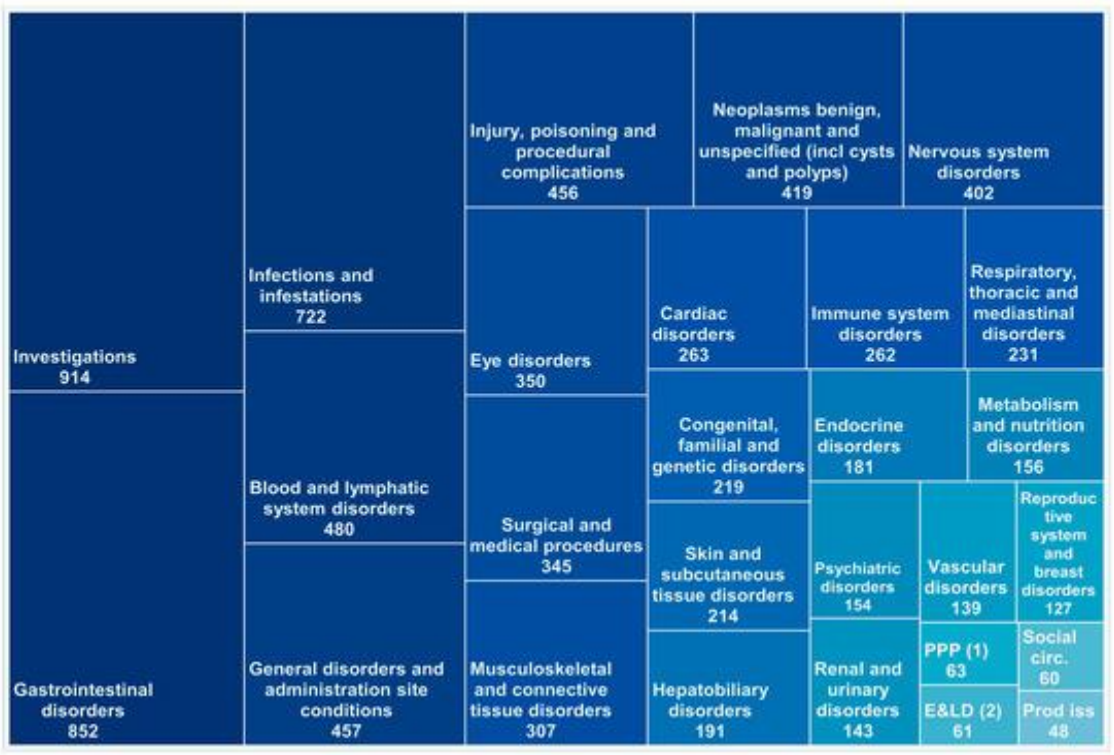


Figure 2. Distribution of AE-PTs across SOC categories (PPP: Pregnancy, puerperium, and perinatal conditions; E&LD: Ear and labyrinth disorders; Prod iss: Product issues).

For each of the twenty-six System Organ Classes (SOCs), the total number of cases linked to PTs within the same SOC was calculated as a percentage of all cases reported for the AC drugs in the PKI group. In the non-PKI group, the proportion of "Infections and Infestations" reached nearly twice the level observed in the PKI group (14.20% versus 6.87%). This finding implies that non-PKI agents carry a substantially elevated risk of infection-related adverse reactions. Both groups displayed elevated frequencies in the "Gastrointestinal Disorders" SOC, with 11.39% for non-PKI drugs and 12.45% for PKI drugs. The "Blood and Lymphatic System Disorders" SOC also showed relatively high proportions in both categories (9.15% for non-PKI and 8.50% for PKI), demonstrating that adverse events in this area can occur with either class of agents. Notably, a larger share of reported AEs in the PKI group (14.57 percent) belonged to the "Investigations" SOC, compared with 9.87% in the non-PKI group. Furthermore, the frequency of events classified under the "Skin and subcutaneous tissue disorders" SOC was approximately twice as high in the PKI group as in the non-PKI group.

Figure 3 illustrates the comparative distribution of frequencies by SOC between the PKI and non-PKI groups.

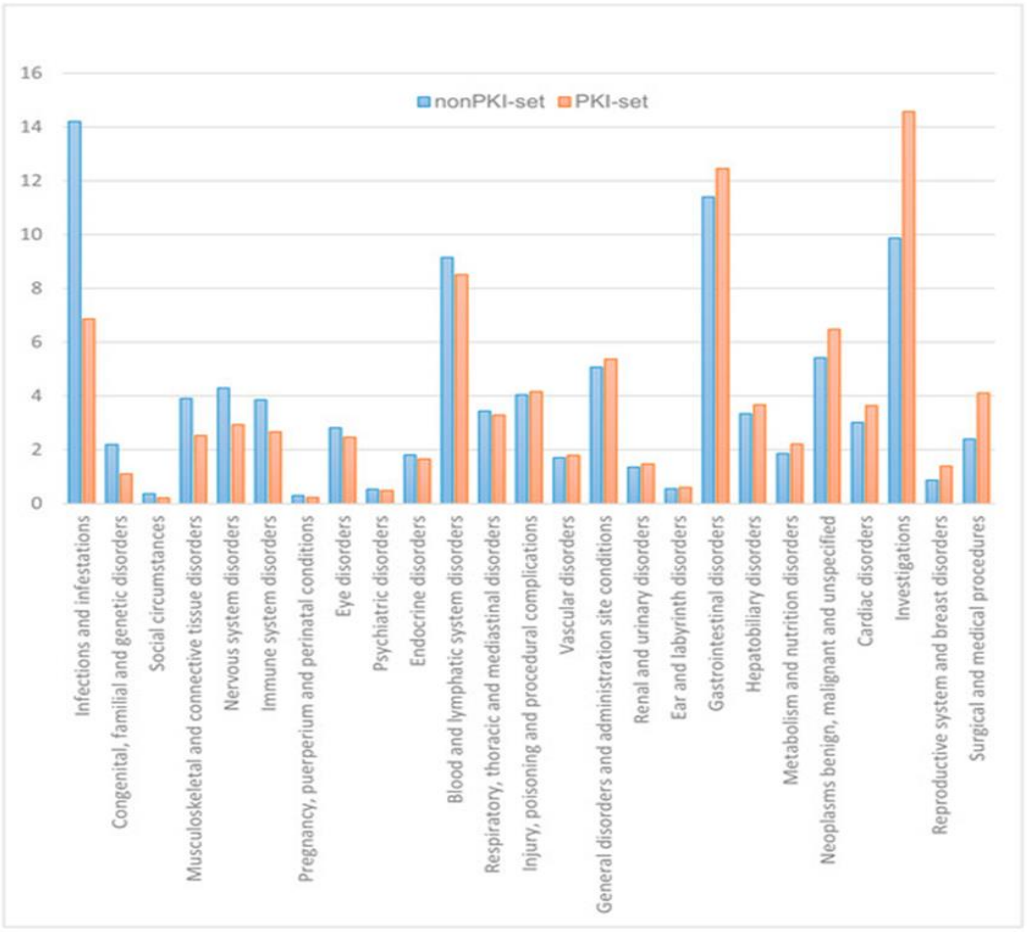


Figure 3. Comparison of frequency distributions by SOC between the PKI group and the non-PKI group.

To determine whether meaningful differences existed in the frequency patterns of individual SOC categories between the PKI and non-PKI groups, a nonparametric independent-samples median test was conducted in SPSS Statistics 26.0. The null hypothesis was rejected for any p-value below 0.05. For each SOC, the average values of all associated AEs were computed separately for the PKI and non-PKI sets. These mean values serve only as descriptive information and were not used in the statistical testing itself. The complete findings from this analysis are summarized in **Table 4.**

Table 4. The adverse events with the largest differences in distribution frequency between the protein kinase inhibitor group and the control.

SOC	Kruskal–Wallis test	Number of PTs -nonPKI	Number of PTs -PKI	nonPKI Mean	PKI Mean
Blood and lymphatic system disorders	P < 0.001	460	244	0.553	0.539
Cardiac disorders	P < 0.001	247	160	0.308	0.554
Congenital, familial and genetic disorders	P < 0.001	210	48	0.067	0.174
Ear and labyrinth disorders	P = 0.204	58	34	0.146	0.206
Endocrine disorders	P < 0.001	162	97	0.167	0.379
Eye disorders	P < 0.001	319	146	0.118	0.414
Gastrointestinal disorders	P < 0.001	806	450	0.960	0.310

General disorders and administration site conditions	P < 0.001	435	203	0.878	2.291
Hepatobiliary disorders	P < 0.001	187	110	0.230	0.364
Immune system disorders	P < 0.001	258	101	0.254	0.289
Infections and infestations	P < 0.001	714	299	0.237	0.399
Injury, poisoning and procedural complications	P < 0.001	415	200	0.601	1.088
Investigations	P < 0.001	829	469	0.299	0.537
Metabolism and nutrition disorders	P < 0.001	143	84	0.352	0.541
Musculoskeletal and connective tissue disorders	P < 0.001	296	128	0.259	0.600
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	P < 0.001	386	189	0.293	0.661
Nervous system disorders	P < 0.001	379	172	0.276	0.545
Pregnancy, puerperium and perinatal conditions	P = 0.010	59	13	0.232	0.061
Product issues	P = 0.203	40	21	0.400	0.302
Psychiatric disorders	P = 0.008	143	53	0.462	0.352
Renal and urinary disorders	P = 0.019	135	74	0.347	0.518
Reproductive system and breast disorders	P < 0.001	101	70	0.50	0.058
Respiratory, thoracic and mediastinal disorders	P < 0.001	222	126	0.275	0.484
Skin and subcutaneous tissue disorders	P < 0.001	194	145	0.409	0.936
Social circumstances	P = 0.168	57	22	0.120	0.284
Surgical and medical procedures	P < 0.001	277	189	0.144	0.354
Vascular disorders	P = 0.233	134	81	0.227	0.467

The majority of SOC categories showed highly statistically significant differences (P < 0.001) between the PKI and non-PKI groups, whereas only a few categories showed no significant difference (P > 0.05). The SOC "General Disorders and Administration Site Conditions" recorded the largest mean value in the PKI group (2.291), which was approximately 2.6 times greater than the corresponding mean in the non-PKI group (0.878). The next-highest values were for the categories "Injury, Poisoning and Procedural Complications" and "Skin and Subcutaneous Tissue Disorders," both approaching 1 and roughly double the levels seen in the non-PKI group. In contrast, "Gastrointestinal disorders" yielded the highest mean in the non-PKI set (0.960) compared with the PKI set (0.310). The categories "Reproductive System and Breast Disorders" and "Pregnancy, Puerperium, and Perinatal Conditions" were particularly noteworthy for their substantially lower mean values in the PKI group compared with the non-PKI group.

Across all SOC categories, the non-PKI group had more PTs than the PKI group, with ratios ranging from 1.3 to 4.5. The reduced number of PTs associated with PKIs likely reflects their more selective mechanism of action and consequently more consistent safety characteristics.

Cluster analysis of the anticancer drugs based on their AE spectrum

Using the furthest-neighbor method with Euclidean distance, the anticancer drugs were organized into 9 distinct clusters. The largest cluster was Cluster 2, which included 26.9% of all drugs (30.6% of PKIs and 23.9% of non-PKIs). This was followed by Cluster 1 (18.8 percent) and Cluster 6 (15.6%). A complete listing of the drugs assigned to each cluster, along with their respective ATC classes, is provided in **Table 5**.

Table 5. Clustering of the anticancer drugs (AC set) using the furthest-neighbour method.

Cluster	Set PKI	ATC Code	Set nonPKI	ATC Code
1	Imatinib	L01EA01	Cyclophosphamide	L01AA01
	Dasatinib	L01EA02	Melphalan	L01AA03
	Nilotinib	L01EA03	Temozolomide	L01AX03
	Alectinib	L01ED03	Methotrexate	L01BA01
	Ruxolitinib	L01EJ01	Pemetrexed	L01BA04
	Ibrutinib	L01EL01	Mercaptopurine	L01BB02

			Fludarabine	L01BB05
			Cytarabine	L01BC01
			Fluorouracil	L01BC02
			Gemcitabine	L01BC05
			Capecitabine	L01BC06
			Vincristine	L01CA02
			Etoposide	L01CB01
			Paclitaxel	L01CD01
			Docetaxel	L01CD02
			Irinotecan	L01CE02
			Doxorubicin	L01DB01
			Epirubicin	L01DB03
			Cisplatin	L01XA01
			Carboplatin	L01XA02
			Oxaliplatin	L01XA03
			Bortezomib	L01XG01
			Celecoxib	L01XX33
			Venetoclax	L01XX52
	Ponatinib	L01EA05	Ifosfamide	L01AA06
	Gefitinib	L01EB01	Bendamustine	L01AA09
	Erlotinib	L01EB02	Busulfan	L01AB01
	Osimertinib	L01EB04	Thiotepa	L01AC01
	Vemurafenib	L01EC01	Carmustine	L01AD01
	Dabrafenib	L01EC02	Dacarbazine	L01AX04
	Crizotinib	L01ED01	Cladribine	L01BB04
	Trametinib	L01EE01	Azacitidine	L01BC07
	Palbociclib	L01EF01	Vinblastine	L01CA01
	Ribociclib	L01EF02	Vinorelbine	L01CA04
	Abemaciclib	L01EF03	Topotecan	L01CE01
2	Lapatinib	L01EH01	Daunorubicin	L01DB02
	Axitinib	L01EK01	Idarubicin	L01DB06
	Acalabrutinib	L01EL02	Mitoxantrone	L01DB07
	Idelalisib	L01EM01	Bleomycin	L01DC01
	Sunitinib	L01EX01	Mitomycin	L01DC03
	Sorafenib	L01EX02	Procarbazine	L01XB01
	Pazopanib	L01EX03	Tretinoin	L01XF01
	Regorafenib	L01EX05	Carfilzomib	L01XG02
	Cabozantinib	L01EX07	Ixazomib	L01XG03
	Lenvatinib	L01EX08	Olaparib	L01XK01
	Nintedanib	L01EX09		
	Bosutinib	L01EA04	Chlorambucil	L01AA02
	Afatinib	L01EB03	Lomustine	L01AD02
	Encorafenib	L01EC03	Clofarabine	L01BB06
	Lorlatinib	L01ED05	Decitabine	L01BC08
	Cobimetinib	L01EE02	Trifluridine	L01BC59
3	Binimetinib	L01EE03	Cabazitaxel	L01CD04
	Tucatinib	L01EH03	Dactinomycin	L01DA01
	Alpelisib	L01EM03	Niraparib	L01XK02
	Midostaurin	L01EX10	Arsenic trioxide	L01XX27
	Gilteritinib	L01EX13	Anagrelide	L01XX35
			Eribulin	L01XX41
4	Ceritinib	L01ED02	Ixabepilone	L01DC04

	Brigatinib	L01ED04	Bexarotene	L01XF03
	Zanubrutinib	L01EL03	Romidepsin	L01XH02
	Vandetanib	L01EX04	Rucaparib	L01XK03
	Ripretinib	L01EX19	Vorinostat	L01XX53
			Enasidenib	L01XX59
			Selinexor	L01XX66
5	Mobocertinib	L01EB10	Streptozocin	L01AD04
			Floxuridine	L01BC09
			Valrubicin	L01DB09
			Adagrasib	L01XX77
6	Asciminib	L01EA06	Nelarabine	L01BB07
	Dacomitinib	L01EB07	Trabectedin	L01CX01
	Selumetinib	L01EE04	Aminolevulinic acid	L01XD04
	Fedratinib	L01EJ02	Alitretinoin	L01XF02
	Pacritinib	L01EJ03	Panobinostat	L01XH03
	Tivozanib	L01EK03	Vismodegib	L01XJ01
	Fruquintinib	L01EK04	Sonidegib	L01XJ02
	Erdafitinib	L01EN01	Talazoparib	L01XK04
	Pemigatinib	L01EN02	Pentostatin	L01XX08
	Larotrectinib	L01EX12	Mitotane	L01XX23
	Entrectinib	L01EX14	Ivosidenib	L01XX62
	Capmatinib	L01EX17	Lurbinectedin	L01XX69
	Avapritinib	L01EX18		
7	Quizartinib	L01EX11	Belinostat	L01XH04
	Pralsetinib	L01EX23	Belzutifan	L01XX74
	Capivasertib	L01EX27		
8	Neratinib	L01EH02	Pralatrexate	L01BA05
	Momelotinib	L01EJ04	Porfimer sodium	L01XD01
	Copanlisib	L01EM02	Glasdegib	L01XJ03
	Duvelisib	L01EM04	Tazemetostat	L01XX72
	Pexidartinib	L01EX15	Sotorasib	L01XX73
	Tepotinib	L01EX21	Eflornithine	L01XX79
	Selpercatinib	L01EX22		
	Umbralisib	L01EX25		
9	Pirtobrutinib	L01EL05	Methyl aminolevulinate	L01XD03
	Infigratinib	L01EN03		
	Futibatinib	L01EN04		

PKI agents were most heavily represented in Cluster 2 (30.6 percent), while non-PKI drugs showed their highest concentration in Cluster 1 (27.3%). Nearly half of all PKIs (48.7%) fell into Clusters 2 and 6 combined, whereas a larger share of non-PKI drugs (50.2%) were spread across Clusters 1 and 2. Clusters 5 and 9 were the smallest, together comprising only 3.1 percent of the total drugs. Cluster 9 displayed a stronger tendency toward PKIs, in contrast to Cluster 5, which consisted mainly of non-PKIs. Overall, the distribution pattern across clusters indicates that neither PKIs nor non-PKIs possess a single characteristic or uniform adverse event profile (**Figure 4**).

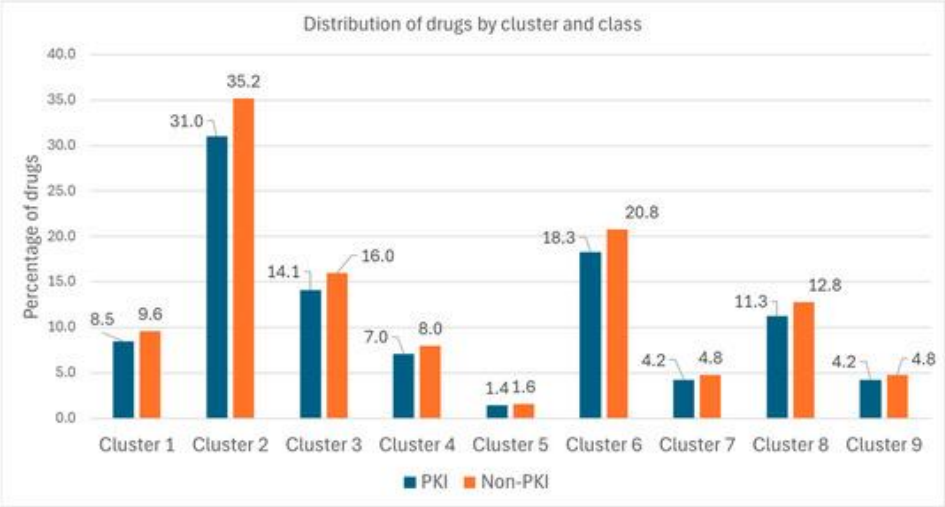


Figure 4. Allocation of anticancer drugs across the identified clusters by category (PKI versus non-PKI).

PKI set

Cyclin-dependent kinase (CDK) inhibitors (L01EF) showed the greatest consistency, with all drugs in this subclass grouped in Cluster 2. In contrast, fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitors (L01EN) were divided, with half assigned to Cluster 6 and half to Cluster 9.

For several PKI categories, roughly half the agents clustered in a single dominant cluster, while the remainder spread across two or three other clusters. This pattern applied to BCR-ABL tyrosine kinase inhibitors (L01EA), where most were in Cluster 1 and the rest divided among Clusters 2, 3, and 6; epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (L01EB), largely in Cluster 2 except for single entries in Clusters 3, 5, and 6; mitogen-activated protein kinase (MEK) inhibitors (L01EE), half in Cluster 3 and a quarter each in Clusters 2 and 6; Janus-associated kinase (JAK) inhibitors (L01EJ), mainly in Cluster 6 with isolated cases in Clusters 1 and 8; and phosphatidylinositol-3-kinase (PI3K) inhibitors (L01EM), primarily in Cluster 8 with a few in Clusters 2 and 3.

B-Raf serine-threonine kinase (BRAF) inhibitors (L01EC) mostly appeared in Cluster 2, and vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (L01EK) predominantly in Cluster 6, each featuring one exception in the other cluster.

Anaplastic lymphoma kinase (ALK) inhibitors (L01ED) showed more diversity, with 40% located in Cluster 4 and individual drugs in Clusters 1, 2, and 3.

A striking observation was that multi-kinase inhibitors classified under L01EX with VEGFR activity strongly favored Cluster 2, mirroring the placement of dedicated VEGFR inhibitors; likewise, multi-kinase compounds targeting PI3K aligned with other PI3K-targeted agents in Cluster 8.

No distinct clustering trend emerged for human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors (L01EH) or Bruton's tyrosine kinase (BTK) inhibitors (L01EL).

Non-PKI set

Every platinum-based compound (L01XA) was assigned to Cluster 1. Half of all antimetabolites (L01B) were also grouped in Cluster 1 — four pyrimidine analogues (capecitabine, cytarabine, fluorouracil, gemcitabine) plus four from folic acid (methotrexate, pemetrexed) and purine analogue (fludarabine, mercaptopurine) subclasses. Half of the plant alkaloids and natural products (L01C) likewise appeared in Cluster 1 (docetaxel, etoposide, irinotecan, paclitaxel, vincristine). Notably, the other two vinca alkaloids (vinblastine and vinorelbine) were found in Cluster 2. Taxanes were divided similarly: docetaxel and paclitaxel in Cluster 1, cabazitaxel in Cluster 3. Among topoisomerase I inhibitors, irinotecan was in Cluster 1 while topotecan was in Cluster 2.

For alkylating agents (L01A), half resided in Cluster 2 (bendamustine, busulfan, carmustine, dacarbazine, ifosfamide, thiotepa), with the remaining 50% split between 25% in Cluster 1, 20% in Cluster 3, and 5% in

Cluster 5. Half of the cytotoxic antibiotics and related substances (L01D) were also in Cluster 2, with the remaining distributed as 20% in Cluster 1 and 10% each in Clusters 3, 4, and 5. Anthracyclines and related substances (L01DB) were split between Cluster 1 (doxorubicin, epirubicin) and Cluster 2 (daunorubicin, idarubicin, mitoxantrone), except for valrubicin alone in Cluster 5. Among proteasome inhibitors (L01XG), bortezomib and carfilzomib favored Cluster 1, whereas ixazomib was in Cluster 2. Hedgehog pathway inhibitors (L01XJ) had sonidegib and vismodegib in Cluster 6, and glasdegib in Cluster 8. Other antineoplastic agents (L01XX) were distributed fairly evenly across Clusters 3, 4, 6, and 8, except for celecoxib and venetoclax in Cluster 1, adagrasib in Cluster 5, and belzutifan in Cluster 7.

No specific cluster preference was detectable for sensitizers used in photodynamic or radiation therapy (L01XD), retinoids for cancer treatment (L01XF), histone deacetylase (HDAC) inhibitors (L01XH), or poly(ADP-ribose) polymerase (PARP) inhibitors (L01XK).

The current work provides an in-depth comparison of tolerability profiles between protein kinase inhibitors (PKIs) and standard non-PKI antineoplastic treatments, based on data from the FAERS database. Assessment of 159 FDA-approved cancer medications encompassing 8,216 distinct Preferred Terms (PTs) revealed notable differences in the breadth and frequency of side effects across the classes. PKIs were linked to a more limited variety of adverse events, averaging 230.1 unique PTs per medication — markedly below the 537.7 average seen with non-PKIs. Bone marrow-related toxicities were considerably less frequent with PKIs, as evidenced by reduced rates of febrile neutropenia (1.93% versus 5.25%), thrombocytopenia (2.18% versus 3.87%), and anemia (2.80% versus 4.09%). This corresponds with the nearly twofold higher proportion of "Infections and Infestations" SOC events in the non-PKI group (14.20% versus 6.87%). Although diarrhea occurred more often with PKIs (13.95% versus 8.36%), the broader "Gastrointestinal disorders" SOC frequency was substantially lower (roughly one-third) compared to non-PKIs. The "Skin and subcutaneous tissue disorders" SOC stood out with distinctly elevated rates in the PKI category. These patterns are consistent with the way PKIs interfere with signaling pathways involved in both malignant growth and normal tissue regulation in the skin and digestive tract. The atypical reporting of "extra dose administered" for ripretinib aligns with emerging recommendations for dose increases upon disease progression [29]. Elevated glucose levels noted with alpelisib and capivasertib are readily attributable to disruption of the AKT signaling cascade [30].

The widespread clinical use of drugs such as celecoxib and methotrexate for non-cancer conditions also influences the greater diversity of unique PTs in the non-PKI group. In the 2022 U.S. prescription rankings, celecoxib ranked 93rd and methotrexate ranked 132nd, while PKIs fell outside the top 300 owing to lower overall use [31].

Even with enhanced targeting, PKIs face important constraints. Resistance development persists as a key issue through mechanisms such as kinase domain alterations, bypass pathway activation, or compensatory kinase increases. Although intended to achieve high specificity, the structural similarity of ATP-binding sites across kinases often leads to unintended interactions and associated toxicities. Pre-treatment kinase mutations can further cause inherent resistance. Increased reporting of central nervous system metastases, metastatic breast cancer, drug resistance, and chronic myeloid leukemia in the PKI group may signal comparatively reduced clinical benefit, frequently due to insufficient use of companion biomarkers or kinase profiling to guide therapy.

Several tactics exist to counteract PKI resistance. Simultaneous use of agents targeting multiple pathways has demonstrated success in reducing resistance emergence and boosting responses across different malignancies by capitalizing on existing medications while addressing their weaknesses [32, 33]. Complementary efforts target underlying molecular processes, such as influencing the tumor microenvironment or applying cutting-edge genetic and epigenetic methods to manage or reverse resistance [34]. Continued progress in these directions is helping precision oncology develop more effective solutions against PKI resistance and deliver better outcomes for patients [35].

The targeted nature of PKIs does not completely prevent off-target actions, largely because ATP-binding domains are highly conserved throughout the kinase family [36, 37]. Managing these side effects typically involves individualized supportive measures to preserve patient compliance and overall well-being throughout therapy. Mean frequency evaluations highlighted both shared AEs across the PKI class and those unique to particular agents — such as reduced vitamin B1 levels linked to fedratinib,

lowered blood glucose with alpelisib and capivasertib, and the administration error "extra dose administered" for ripretinib, which is consistent with current clinical recommendations for increasing dosage after disease advancement.

In comparison, the majority of conventional chemotherapeutic drugs, which possess broader mechanisms of action, were connected with a wide variety of body-wide adverse reactions capable of substantially diminishing patients' quality of life. Clear distinctions also emerged at the SOC level, with non-PKIs associated with elevated infection rates, suggesting a stronger immunosuppressive potential that may complicate disease management and require adjusted care strategies [38]. These results are consistent with the higher incidence of neutropenia in the non-PKI group compared with the PKI group [39]. SOC analysis further revealed approximately twice the event reporting frequency in the "Skin and subcutaneous tissue disorders" category for PKIs. Clustering results reinforced this observation: most multi-kinase inhibitors under L01EX with VEGFR activity clustered in Cluster 2 alongside dedicated VEGFR agents and showed at least one PT in the "Skin and subcutaneous tissue disorders" SOC with a frequency exceeding 1%. Such skin reactions are thought to arise from EGFR blockade in basal keratinocytes and hair follicles — cells that, like many tumor cells, highly express EGFR [40].

Unlike prior investigations examining the overall PKI category [41], the present study delivers a more detailed examination focused specifically on PKIs applied in cancer treatment. While earlier work grouped agents by their primary molecular targets, this analysis prioritizes ATC classification. It also utilizes a more relevant comparator group of non-PKI oncology drugs rather than randomly chosen medications.

Although FAERS provides useful real-world evidence, it carries inherent limitations and potential biases. As a voluntary reporting database, it is prone to underreporting and selective reporting, especially for heavily prescribed drugs such as methotrexate and celecoxib. This study did not account for differences in drug utilization volume, concurrent therapies, or length of treatment — factors that can affect AE reporting rates — yet such influences are expected to impact both drug classes similarly. All PTs were weighted equally regardless of severity, which may overemphasize common mild reactions (e.g., diarrhea) while underrepresenting infrequent but serious toxicities (e.g., febrile neutropenia). The central goal was to determine whether the selective mechanism of protein kinase inhibitors results in a narrower range of adverse reactions.

Clustering outcomes showed that drugs sharing an ATC class often group due to overlapping molecular actions, yet the strength of this grouping differs considerably. Some therapeutic classes formed tight clusters, while others were more dispersed, indicating that additional elements beyond mechanism of action shape their safety characteristics. For most classes, the primary pharmacological target was an inconsistent predictor of overall toxicity patterns.

Although PKIs represent an encouraging advance with a relatively more focused safety profile, careful monitoring and proactive handling of their characteristic side effects remain essential. Ongoing pharmacovigilance and real-world evidence reviews will be vital for further optimizing treatment protocols and achieving better balances between efficacy and tolerability.

Conclusion

This study offers a refined perspective on the intricate safety profiles of protein kinase inhibitors compared with traditional cytotoxic anticancer agents. Despite their improved precision, PKIs are associated with distinctive adverse reactions, mainly involving the skin and gastrointestinal system, stemming from their interactions with various kinase-dependent pathways. These insights can help clinicians personalize cancer therapy by matching treatments more closely to each patient's risk profile, thereby improving outcomes. Moreover, recognizing PKI-specific side effects may inform the design of next-generation inhibitors with enhanced safety margins. Overcoming resistance driven by kinase mutations will require continued development of novel combination and precision strategies. In summary, this comparative evaluation underscores the critical role of individualized treatment planning in oncology to maximize therapeutic benefit while reducing harm.

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