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CLINICAL RESEARCH
Arrhythmias

Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study

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Aims With the explosion of anticancer drugs, an emerging concern is the risk for drug-induced sudden death (SD) via ventricular arrhythmias (VA).

Methods and results We used the international pharmacovigilance database VigiBase ($n = 18\,441\,659$ reports) to compare drug-induced long QT (diLQT, $n = 18\,123$) and VA ($n = 29\,193$) including torsade de pointes (TdP, $n = 8163$) reporting for 663 anticancer drugs vs. all other drugs until 01/01/2019. The analysis used the 95% lower-end credibility interval of the information component (IC_{025}), an indicator for disproportionate Bayesian reporting; significant when $IC_{025} > 0$. There were 2301 reports (13.8% fatal) for 40 anticancer drugs significantly associated with diLQT (with 27 also associated with VA or SD) and 9 drugs associated with VA without diLQT. Half of these (46.9%, 23/49) were associated with SD. Most (41%, 20/49) were kinase inhibitors, 8% (4/49) were hormonal therapies, 6% (3/49) were immunotherapies, 24% (12/49) were cytotoxics, and 20% (10/49) were miscellaneous. In VigiBase, reports of diLQT, TdP, or VA increased from 580 in the period 1967–83 to 15 070 in 2014–18 with the proportion related to anticancer drugs increasing from 0.9% (5/580) to 14.0% (2115/15 070) ($P < 0.0001$). Concordance between these VigiBase signals and data concerning diLQT and VA/TdP identified in CredibleMeds or US Food and Drug Administration (FDA) labels was moderate ($\kappa = 0.47$ and 0.40, $P < 0.0001$). Twenty-three drugs represent new signals, while 24 flagged by CredibleMeds or FDA had no signal in VigiBase. A three-level SD risk stratification relying on isolated long QT (low risk), associated with VA without SD (moderate risk), and VA with SD (high risk) is proposed.

Conclusion This list of liable anticancer drugs may prove useful for physicians and regulatory authorities to re-evaluate cardiac monitoring requirements.

Clinical trial registration NCT03530215.

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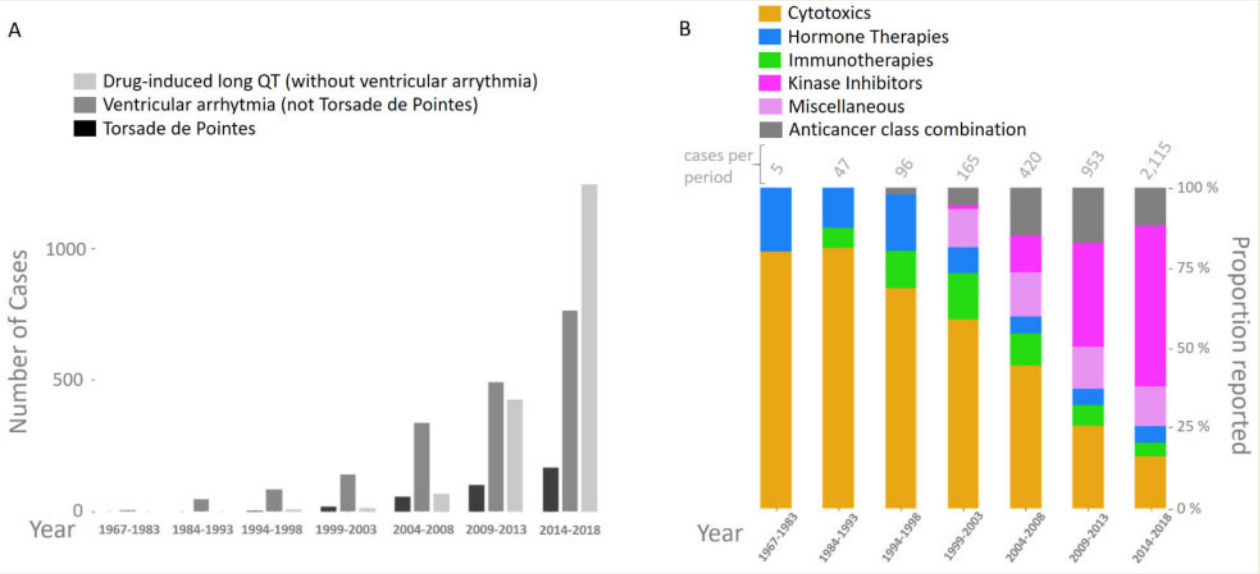
Graphical Abstract



Evolution of reporting for drug-induced long QT, ventricular arrhythmias, and torsade de pointes associated with anticancer drugs (*A*) as a function of their classes (*B*) in VigiBase from inception (1967) to January 2019.

Keywords Disproportionality analysis • Anticancer drugs • Long QT • Ventricular arrhythmias • Pharmacovigilance • Torsade de pointes

Introduction

The development of cancer therapeutics has resulted in a better prognosis and long-term survival for patients with many malignancies.[1] Anticancer drugs may also lead to severe cardiovascular adverse drug reactions (ADR) carrying a high morbidity burden and can be fatal.[2] This interplay between cancer and heart conditions is the subject of the booming field of cardio-oncology. Cardiac ADR of cytotoxic anticancer drugs have been identified for decades, such as anthracycline-induced heart failure or acute myocardial infarction with anti-metabolites.[2,3] With the exponential development of new classes of anticancer drugs [including immunotherapy and kinase inhibitors (KI)], other heart-related ADR have emerged and represent an important concern for regulatory agencies, companies, and patient care providers. A striking example is the increased reporting of myocarditis (fatality rate ~30–50%) occasionally induced by immune checkpoint inhibitors, which are breakthrough therapeutics approved in a wide variety of cancers.[4,5] Cardiac arrhythmias are another emerging and poorly characterized concern of anticancer drugs with an increasing number of targeted therapies such as KI and anti-hormonal agents prolonging QT interval, a well-recognized marker of increased risk for cardiac arrhythmias and sudden death (SD).[6,7]

The QT interval on the electrocardiogram (ECG), corrected for heart rate (QTc), is a measure of the duration of ventricular repolarization and is a widely used proxy of the drug-induced ventricular arrhythmia (VA) risk.[8] It remains the recommended standard surrogate used in human studies, despite its well-recognized limitations.[9] Many drugs slightly prolong the QT interval, but in some patients, this prolongation can be exaggerated and provoke the morphologically distinctive polymorphic VA torsade de pointes (TdP). Symptoms associated with TdP include syncope and SD if the arrhythmia is prolonged or degenerates into ventricular fibrillation. More recently, it has been reported that some anticancer drugs, such as ibrutinib (a Bruton KI), can also lead to fatal VA without prolonging QT.[10]

Using VigiBase, the World Health Organization's (WHO) global pharmacovigilance database, we aimed to better define and risk stratify these severe cardiac arrhythmia ADR to improve patient safety and facilitate monitoring guidelines after the administration of anticancer drugs. We also sought to identify new drugs with signals for VA, long QT, and TdP, which were not previously identified during clinical trials.

Methods

Study design and data sources

This observational, retrospective, pharmacovigilance study is a disproportionality analysis based on ADR reported in VigiBase, the WHO deduplicated database of individual case safety reports (i.e. reports thereafter).[11] VigiBase is managed by the Uppsala Monitoring Centre (UMC, Uppsala, Sweden) and contains ~19 million reports (through January 2019) submitted by national pharmacovigilance centres since 1967. The use of confidential, electronically

processed patient data was approved by the Vanderbilt University Medical Center institutional review board (# 181337, USA).

Procedures

This study included all drug-induced long QT (diLQT), TdP, or VA classified by group queries according to the Medical Dictionary for Regulatory Activities (Supplementary material online, *Table S1*), between inception on 14 November 1967 and 1 January 2019. DiLQT, TdP, or VA specifically assessed in the analysis were those reported as suspected to be caused by a drug (vs. concomitant use). Each report contains general administrative information (country of origin, date of reporting, and reporter qualification), patient characteristics (sex, age), drugs (indication, start and end dates of administration, dosage regimen, and route of administration), and reactions or events (reported terms, onset and end date, seriousness, and final outcome). A severe ADR was defined as causing death, being life-threatening, requiring hospital stay (initial or prolonged), or leading to persistent or clinically significant disability, congenital anomaly, birth defect, or any other medically important conditions.

Statistical analysis

VigiBase allows disproportionality analysis (also known as case–non-case analysis), which we used to assess whether suspected diLQT, TdP and VA were differentially reported with each drug (663 individual molecules pertaining to the anticancer drugs) vs. the full database of 20 222 drugs (Supplementary material online, *Figure S1* for the flow chart). Disproportionality analyses compare the proportion of a selected specific ADR reported for a single drug with the proportion of the same ADR for a control group of drugs (i.e. full database with all drugs). The denominator in these analyses is the total number of ADR reported for each group of drugs. If the proportion of cases associated with a specific drug is greater than in patients without this ADR (non-cases), there is a disproportional association (signal identification) between the ADR and the drug.[5] We calculated a Bayesian disproportionality estimate suitable when taking the full database as comparator, i.e. the information component (IC). IC compares observed and expected number of reports for drug-ADR pairs. The IC_{025} is the lower end of the 95% credibility interval for the IC so a positive value of the IC_{025} is deemed significant. More information concerning calculation of the IC/IC_{025} is provided in the Supplementary material online, *Methods*, and these methods have been recently used in similar settings and detailed elsewhere.[5,10,12,13] Since this work focused on identifying culprit anticancer drugs, we further performed a sensitivity analysis and estimated the frequentist disproportionality association [reporting odds ratio (ROR)] with diLQT, TdP, VA, and SD for each anticancer drug already flagged with positive IC_{025}, restricting the background database to reports associated with at least one anticancer drugs (defined as drugs pertaining to the anatomical therapeutic classification L: antineoplastic and immunomodulating agents). ROR was calculated by Chi2 test, and the 95% confidence interval ($CI_{95\%}$) was estimated, as previously described.[5,14] A lower end of the ROR $CI_{95\%} \geq 1$ is considered statistically significant.

Characteristics of reports in VigiBase were described in terms of means ± standard deviation or medians and interquartile range [IQR] for quantitative variables, and in terms of numbers and proportion for qualitative ones. Comparisons were performed by Chi^2 test and Wilcoxon test with Dunn's post-tests, as appropriate. $P < 0.05$ was deemed statistically significant.

Concordance (agreement) between the data describing liability of anticancer drugs to induce cardiac arrhythmias according to VigiBase vs. US Food and Drug Administration (FDA) labels (accessible at https://www.accessdata.fda.gov/scripts/cder/daf/) and CredibleMeds® (accessible at www.crediblemeds.org) was computed using the Cohen kappa coefficient.

Results

Trends in anticancer drug-associated cardiac arrhythmia reporting over decades

The study included 42 462 reports of diLQT, TdP, or VA from VigiBase inception, through 1 January 2019. The number increased from 580 in the period 1967–83 to 15 070 for 2014–18 (Supplementary material online, *Figure S2*). The corresponding proportion related to anticancer drugs increased from 0.9% (5/580) to 14.0% (2115/15 070) ($P < 0.00001$). Anticancer drugs were divided into five subgroups: cytotoxic treatments (CT, including antimetabolites and anthracyclines), hormone therapies (HT), immunotherapies (IT, including immune-related cell therapies), KI (including any drug interacting directly with a kinase protein or its ligands), and other therapies [miscellaneous (Misc)]. The majority of this increase in reporting over years was in the KI group (*Graphical abstract*) representing 51.6% (1091/2115) of these cardiac arrhythmia reports associated with anticancer drugs within the 2014–18 period vs. 14.7% (311/2115) with CT, 5.9% (124/2115) with HT, 2.5% (52/2115) with IT, and 12.5% (265/2115) with a combination of any of these anticancer classes (Combo; i.e. one drug or more pertaining to at least two of these classes: CT, HT, IT, KI, Misc) ($P < 0.00001$).

Anticancer drugs associated with long QT and VA including TdP and SD

Forty anticancer drugs were significantly associated with diLQT (including 27 also associated with VA or SD) and 9 with VA without diLQT when taking as background either the full database ($n = 18\,441\,659$; $IC_{025} > 0$) or when restricting the database to cases involving at least one anticancer drug used ($n = 4\,197\,602$; ROR $CI_{95\%} \geq 1$) (*Table 1*). Most (41%, 20/49) were KI, 24% (12/49) were CT, 8% (4/49) were HT, 6% (3/49) were IT, and 20% (10/49) were Misc. Details regarding the magnitude of the association by drug and per subtype of arrythmia (diLQT, VA and TdP) and signals for SD are shown in *Table 1*. Details concerning the year for which these anticancer drugs were first significantly associated with any of these cardiac arrhythmias are shown in Supplementary material online, *Figure S2*. Details concerning number of reports per year of these cardiac arrhythmias are shown in *Figure 1*. To further evaluate the seriousness of these cardiac events (diLQT, VA including TdP), we stratified the 49 drugs of interest as a function of the presence or not of a significant association with drug-induced SD (*Table 2*). Half of these anticancer drugs (46.9%, 23/49) were associated with SD. We generated a three-level SD risk stratification (*Figure 2*) constituted of drugs associated with only isolated diLQT without VA nor SD (low risk, $n = 13$), drugs associated with VA without SD (moderate risk, $n = 13$), and drugs associated with VA and SD (high risk, $n = 23$). Among anticancer drugs with moderate and high risk for SD, most were also associated with diLQT (75%, 27/36) but not all (25%, 9/36). The top three drugs with the highest disproportional association

Table 1 Anticancer drugs associated with at least one of the following adverse drug reactions: drug-induced long QT syndrome, torsade de pointes, and ventricular arrhythmias based on disproportionality analysis in VigiBase (through 01 January 2019)

Drug	Class	N_{drug}	diLQT (N_{effect}[a] = 3036)			TdP[b] (N_{effect}[a] = 761)			VA (N_{effect}[a] = 3748)			SD (N_{effect}[a] = 13 288)		
			N_{obs}	IC_{025}	*r*OR [$CI_{95\%}$]	N_{obs}	IC_{025}	*r*OR [$CI_{95\%}$]	N_{obs}	IC_{025}	*r*OR [$CI_{95\%}$]	N_{obs}	IC_{025}	*r*OR [$CI_{95\%}$]
Amsacrine[d]	CT	287	5	1.3	25 [10–59]	3	0.4	58 [19–183]	14	3.1	58 [34–99]	10	1.5	11.4 [6.1–21.4]
Capecitabine[c,d]	CT	49 174							161	0.8	3.8 [3.2–4.4]	319	0.3	2.1 [1.9–2.3]
Clofarabine[c,d]	CT	2216	5		3.1 [1.3–7.5]	2		5 [1.2–20]	11	0.5	5.6 [3.1–10]	57	2.0	8.3 [6.4–10.9]
Combretastatin a4	CT	25	3	0.7	189 [56–630]	1		230 [31–1703]	1		47 [6.3–345]			
Cytarabine[c,d]	CT	26 300	52	0.6	2.8 [2.1–3.6]	14		3 [1.8–5]	89	0.8	3.9 [3.1–4.8]	358	1.4	4.4 [4–4.9]
Daunorubicin[c,d]	CT	6655	28	1.4	5.9 [4.1–8.5]	9	0.4	7.5 [3.9–15]	52	1.8	8.9 [6.8–12]	149	2.0	7.3 [6.2–8.6]
Decitabine[c,d]	CT	2894	10	0.6	4.8 [2.6–8.9]							22		2.4 [1.6–3.7]
Fluorouracil[c,d]	CT	65 547							138	0.2	2.4 [2–2.9]	383	0.2	1.9 [1.7–2.1]
Idarubicin[c,d]	CT	3539	12	0.7	4.7 [2.7–8.3]	5		7.8 [3.3–19]	18	0.9	5.7 [3.6–9.1]	42	0.9	3.8 [2.8–5.1]
Mitoxantrone[c,d]	CT	4847	12	0.3	3.4 [1.9–6.1]	9	0.8	10 [5.4–20]	28	1.2	6·5 [4.5–9.5]	60	1.0	4 [3.1–5.1]
Nelarabine[c,d]	CT	370							4	0.3	12 [4.6–33]			
Pegaspargase[c,d]	CT	4481							22	0.9	5.5 [3.6–8.4]	146	2.5	10.7 [9.1–12.6]
Bicalutamide[c,d]	HT	4802	13	0.5	3.8 [2.2–6.5]	10	1.0	12 [6.2–22]	23	0.9	5.4 [3.6–8.2]	24		1.6 [1.1–2.4]
Letrozole[c,d]	HT	15 564	25	0.1	2.2 [1.5–3.3]									
tamoxifen[c,d]	HT	18 567	28	0.0	2.1 [1.4–3]	8		2.4 [1.2–4.8]						
Toremifene[c,d]	HT	258	2		11 [2.7–43]	1		21 [3–153]	4	0.6	18 [6.6–47]	8	1.2	10.1 [5–20.4]
Aldesleukin[c,d]	IT	1553							15	1.6	11 [6.6–18]	29	1.4	6 [4.2–8.7]
Axicabtagene ciloleucel[c,d]	IT	117							4	1.0	40 [15–108]	3		8.3 [2.6–26.1]
Interferon alfacon-1[e]	IT	742							5	0.2	7.6 [3.2–18]			
Alectinib[c,d]	KI	1346	5	0.1	5.2 [2.1–12]									
Bosutinib[c,d]	KI	2927	9	0.4	4.3 [2.2–8.2]									
Ceritinib[c,d]	KI	1747	21	2.6	17 [11–26]	2		6.3 [1.6–25]						
Cobimetinib[c,d]	KI	1496	20	2.7	19 [12–29]									
Crizotinib[c,d]	KI	7614	102	3.4	19 [16–24]	9	0.2	6.6 [3.4–13]						
Dabrafenib[c,d]	KI	7612	27	1.2	5 [3.4–7.2]									
Dasatinib[c,d]	KI	19 654	94	1.9	6.8 [5.6–8.4]									
Enzastaurin	KI	138	1		10 [1.4–72]				3	0.2	25 [7.9–78]	2		4.6 [1.1–18.7]
Ibrutinib[c,d]	KI	21 110							99	1.3	5.4 [4.4–6.6]	126	0.1	1.9 [1.6–2.3]
Imatinib[c,d]	KI	44 671	64	0.2	2 [1.6–2.6]									
Lenvatinib[c,d]	KI	2555	11	1	6 [3.3–11]									
Midostaurin[c,d]	KI	1001	34	4	49 [35–69]	2		11 [2.8–44]	4		4.5 [1.7–12]			
Nilotinib[c,d]	KI	17 471	369	4.2	34 [30–38]	18	0.4	5.8 [3.6–9.3]	46	0.3	3 [2.2–4]	92		1.7 [1.4–2.1]
Osimertinib[c,d]	KI	2423	37	3.2	22 [16–30]	4		9.2 [3.4–24]						
Pazopanib[c,d]	KI	19 816	40	0.5	2.8 [2.1–3.9]	14		4 [2.3–6.7]						
Ribociclib[c,d]	KI	1738	105	5.3	92 [75–112]	4	0.1	13 [4.8–34]						
Sunitinib[c,d]	KI	29 774	71	0.9	3.4 [2.7–4.2]	12		2.2 [1.3–4]				130		1.4 [1.2–1.6]
Trametinib[c,d]	KI	7538	26	1.1	4.8 [3.3–7.1]									
Vandetanib[c,d]	KI	971	97	5.8	158 [128–196]	10	2.5	58 [31–109]	10	1.3	12 [6.3–22]			
Vemurafenib[c,d]	KI	8322	106	3.3	18 [15–22]									
Arsenic trioxide[c,d]	Misc	1642	115	5.5	108 [89–131]	14	2.7	48 [28–82]	25	2.4	17 [12–26]	20	0.6	3.9 [2.5–6]
Belinostat[c,d]	Misc	61	3	0.6	72 [22–228]									
Carfilzomib[c,d]	Misc	8109	19	0.5	3.3 [2.1–5.1]				18		2.5 [1.6–4]	59	0.3	2.3 [1.8–3]
Chidamide	Misc	238	7	2.1	42 [20–89]									
Gemtuzumab ozogamicin[c,d]	Misc	1729	9	1	7.2 [3.8–14]	3		9.6 [3.1–30]	8	0.2	5.2 [2.6–10]	34	1.5	6.3 [4.5–8.9]

Continued

Table I *Continued*

Drug	Class	N_{drug}	diLQT (N_{effect}[a] = 3036)			TdP[b] (N_{effect}[a] = 761)			VA (N_{effect}[a] = 3748)			SD (N_{effect}[a] = 13 288)		
			N_{obs}	IC_{025}	*r*OR [$CI_{95\%}$]	N_{obs}	IC_{025}	*r*OR [$CI_{95\%}$]	N_{obs}	IC_{025}	*r*OR [$CI_{95\%}$]	N_{obs}	IC_{025}	*r*OR [$CI_{95\%}$]
Mogamulizumab[c,d]	Misc	497							5	0.6	11 [4.7–27]			
Panobinostat[c,d]	Misc	1483	24	3	23 [15–34]									
Romidepsin[c]	Misc	462	11	2.6	34 [19–62]	2		24 [6–97]	4	0.1	9.8 [3.7–26]	4		2.8 [1–7.4]
Tretinoin[c,d]	Misc	5250	14	0.4	3.7 [2.2–6.3]	3		3.2 [1–9.8]						
Vorinostat[c,d]	Misc	1378	23	3	24 [16–36]	6	1.2	24 [11–54]	7	0.2	5.7 [2.7–12]	24	1.2	5.6 [3.7–8.4]

Associations were deemed significant when the lower end of the 95% credibility interval was positive (IC_{025} >0) for analysis vs. full database (n = 18 441 659); or when the lower end of the 95% confidence interval of the reporting odds ratio was >1 (rOR_{025} >1) for analysis restricted to reports with anticancer drugs as background (n = 4 197 602). Non-significant associations are not represented. Results with SD are also represented for these latter drugs.

ADR, adverse drug reactions; $CI_{95\%}$, 95% confidence interval; CT, chemotherapy; diLQT, drug-induced long QT syndrome; HT, hormonotherapy; IT, immunotherapy; KI, kinase inhibitor; Misc, miscellaneous; N_{drug}, number of reports for the drug; N_{obs}, number of reports observed for the ADR with the drug of interest; SD, sudden death; TdP, torsade de pointes; VA, ventricular arrhythmias.

[a]N_{effect} refers to the number of reports for the ADR of interest in the anticancer group. The N_{effect} in the full database background is 18 123 for diLQT; 8163 for TdP; 29 193 for VA; and 85 350 for SD.

[b]Data of disproportionality for TdP breakdown (vs. VA) was considered only for drugs with a positive signal for diLQT.

[c]Available on the US market.

[d]Available on the European market.

[e]Withdrawn from the US market,

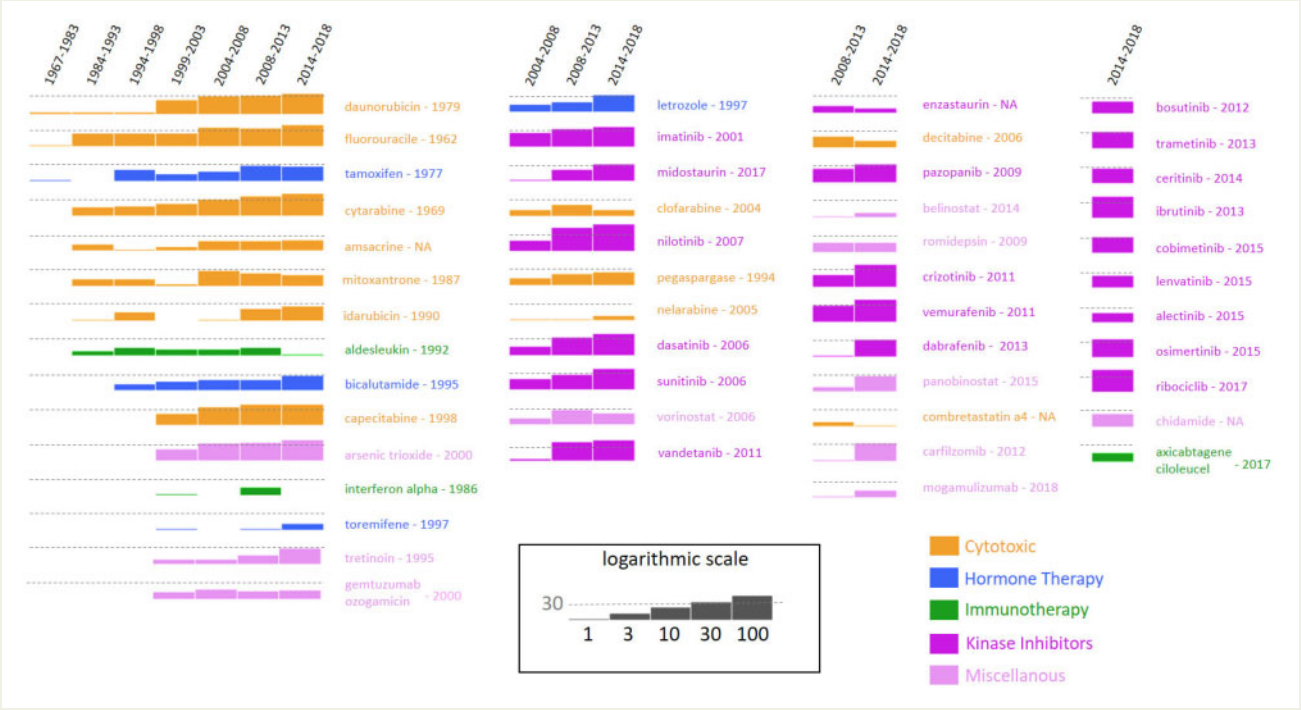


Figure 1 Evolution of the absolute number of long QT syndrome and/or ventricular arrhythmias including torsade de pointe reports over time for each of the 49 culprit anticancer drugs identified using VigiBase (see *Table 1*). For each drug, the year of Food and Drug Administration approval was added when available (otherwise, NA stands for not available).

(*Table 1* and Supplementary material online, *Figure S3*, using IC_{025}) with diLQT were vandetanib (KI, n = 97, IC_{025} = 5.8, year of FDA approval 2011), arsenic trioxide (Misc, n = 115, IC_{025} = 5.5, year of FDA approval 2000), and ribociclib (KI, n = 105, IC_{025} = 5.3, year of FDA approval 2017). This was concordant with arsenic trioxide (n = 14, IC_{025} = 2.7), vandetanib (n = 10, IC_{025} = 2.5), and vorinostat (Misc,

Table 2 Classification of the 49 anticancer drugs as a function of the signals identified in VigiBase for drug-induced long QT syndrome, ventricular arrhythmias including torsade de pointes, and sudden death

Drug	Class	Subclass	Target/mechanism
diLQT			
VA or TdP and sudden death			
Amsacrine	CT	Anthracycline and derivatives	Topoisomerase II
Daunorubicin	CT	Anthracycline and derivatives	Topoisomerase II
Idarubicin	CT	Anthracycline and derivatives	Topoisomerase II
Mitoxantrone	CT	Anthracycline and derivatives	Topoisomerase II
Clofarabine	CT	Antimetabolite	Purine analog
Cytarabine	CT	Antimetabolite	Cytidine analog
Decitabine[a]	CT	Antimetabolite	Hypomethylating agent/cytidine analog
Bicalutamide	HT	Antiandrogen	Androgen receptor
Toremifene	HT	SERM	Estrogen receptor
Enzastaurin	KI	Kinase inhibitor	PKCβ, AuroraA/B, Chk1/2, URACα, and PI3Kα
Nilotinib	KI	Kinase inhibitor	BCR-ABL, PDGFR, KIT, CSF-1R, and DDR1
Sunitinib	KI	Kinase inhibitor	VEGFR1/2/3, PDGFRα/β, KIT, FLT3, CSF-1R, and RET
Arsenic trioxide	Misc	Other small molecule	PML/RAR-alpha
Carfilzomib	Misc	Other small molecule	Proteasome inhibitors
Romidepsin	Misc	Epigenetic inhibitor	Histone deacetylase
Vorinostat	Misc	Epigenetic inhibitor	Histone deacetylase
Gemtuzumab ozogamicin	Misc	Antibody drug conjugate	CD33
VA or TdP without sudden death			
Combretastatin a4	CT	Vascular disruptive agent	Vascular endothelial cells
Tamoxifen	HT	SERM	Estrogen receptor
Ceritinib	KI	Kinase inhibitor	ALK, IGF-1R, InsR, and ROS1
Crizotinib	KI	Kinase inhibitor	ALK, ROS1, Met, RON
Midostaurin	KI	Kinase inhibitor	FLT3, KIT ,PDGFRα/β, VEGFR2, and PKC
Osimertinib	KI	Kinase inhibitor	EGFRm (19 indel, L858R, T790M)
Pazopanib	KI	Kinase inhibitor	VEGFR1/2/3, PDGFRα/β, KIT, FGFR1/3, ITK, LCK, FMS
Ribociclib	KI	Kinase inhibitor	CDK4/6
Vandetanib	KI	Kinase inhibitor	EGFR, VEGFR, RET, BRK, TIE2, EPHR, and SRC
Tretinoin	Misc	Other small molecule	PML/RAR-alpha
No VA, TdP, nor sudden death			
Letrozole	HT	Aromatase inhibitor	Estrogen receptor
Alectinib	KI	Kinase inhibitor	ALK and RET
Bosutinib	KI	Kinase inhibitor	BCR-ABL, Src, Lyn, and Hck
Cobimetinib	KI	Kinase inhibitor	MEK1, MEK2
Dabrafenib	KI	Kinase inhibitor	BRAF V600/wt, CRAF, SIK1, NEK11, and LIMK1
Dasatinib	KI	Kinase inhibitor	BCR-ABL, SRC, LCK, YES, FYN, c-KIT, EPHA2, and PDGFRβ
Imatinib	KI	Kinase inhibitor	BCR-ABL, PDGFR, SCF, and KIT
Lenvatinib	KI	Kinase inhibitor	VEGFR1/2/3, PDGFRα, KIT, FGFR1/2/3/4, and RET
Trametinib	KI	Kinase inhibitor	MEK1, MEK2
Vemurafenib	KI	Kinase inhibitor	BRAF, CRAF, ARAF, SRMS, ACK1, MAP4K5, and FGR
Belinostat	Misc	Epigenetic inhibitor	Histone deacetylase
Chidamide	Misc	Epigenetic inhibitor	Histone deacetylase
Panobinostat	Misc	Epigenetic inhibitor	Histone deacetylase
No diLQT			
VA with sudden death			
Capecitabine	CT	Antimetabolite	Uracil analogue
Fluorouracil	CT	Antimetabolite	Uracil analogue
Pegaspargase	CT	Other protein-based therapies	L-Asparagine
Aldesleukin	IT	Cytokine	Interleukin-2
Axicabtagene ciloleucel	IT	CAR T cell	CD19
Ibrutinib	KI	Kinase inhibitor	BTK

Continued

Table 2 *Continued*

Drug	Class	Subclass	Target/mechanism
VA without sudden death			
Nelarabine	CT	Antimetabolite	Guanosine analogue
Interferon alfacon-1	IT	Cytokine	Interferon
Mogamulizumab	Misc	Chemokine receptor inhibitor	CCR4

CAR, chimeric antigen receptor; CT, chemotherapy; diLQT, drug-induced long QT syndrome; HT, hormonotherapy; IT, immunotherapy; KI, kinase inhibitor; MAB, monoclonal antibody; Misc, miscellaneous; SD, sudden death; SERM, selective oestrogen receptor modulator; VA, ventricular arrhythmias; TdP, torsade de pointes.
[a]Decitabine was significantly associated with diLQT and SD, but not with TdP nor VA.

$n = 6$, $IC_{025} = 1.2$, year of FDA approval 2006) carrying the highest association with TdP. The top three drugs associated with VA were amsacrine (CT, $n = 14$, $IC_{025} = 3.1$), arsenic trioxide ($n = 25$, $IC_{025} = 2.4$), and daunorubicin (CT, $n = 52$, $IC_{025} = 1.8$, year of FDA approval 1979). The top drugs in terms of absolute number of reports were respectively nilotinib for diLQT (KI, $n = 369$, $IC_{025} = 0.4$, year of FDA approval 2007), TdP ($n = 18$, $IC_{025} = 0.4$), and capecitabine for VA (CT, $n = 161$, $IC_{025} = 0.8$, year of FDA approval 1998) (*Table 1* and *Figure 1*). The major mechanisms of action of these drugs are detailed in *Table 2*.

Of note, we further validated this disproportionality method using positive and negative controls in terms of drugs at known risk of diLQT and TdP [dofetilide, sotalol, ibutilide with IC_{025} values among the highest (4.9–5.82)] vs. protective for diLQT and TdP (progesterone, levonorgestrel, and testosterone carrying among the lowest IC_{025} values).[7,9,15] These data are shown in Supplementary material online, *Figure S3* and the top 25 highest and lowest IC_{025} values for diLQT among all drugs available in VigiBase are shown in Supplementary material online, *Tables S2 and S3*.

Clinical features of cardiac arrhythmias associated with anticancer drugs in VigiBase

Clinical characteristics derived from the 2301 reports (diLQT without TdP, $n = 1406$; TdP, $n = 196$, and VA without TdP, $n = 699$) associated with the 49 anticancer drugs of interest are displayed in *Table 3* and in Supplementary material online, *Table S4*. Overlap between culprit anticancer drug classes within these reports is represented in *Figure 3*. The median age was 63 years (IQR 51–71). Male predominance was found in VA reports excluding TdP (64.9%, 431/664), contrasting with female predominance in diLQT and TdP reports (51.4%, 698/1359, $P < 0.0001$). Most reports were in the last 5 years (1434/2301, 62%) and were by healthcare professionals (1701/1943, 88%) in America (1038/2301, 45%) or Europe (762/2301, 33%). Most reports involved at least one culprit KI (64%, 1477/2301). A majority of reports were considered serious (94%, 1946/2078). All-cause fatality was 13.8% (317/2301) and 10% reported SD (228/2301, *Table 3*). The final outcome after stopping the culprit anticancer drug was available for 397 reports, of which 326/397 (82%) resolved. Most patients (49%, 766/1555) had hematological diseases, particularly chronic myeloid leukaemia (23%, 363/1555) or other leukaemia (17%, 272/1555). Among solid tumors, the most represented were colorectal, lung, breast, and kidney cancers (8.1%, 126/1555; 7.3%, 114/1555; 6.7%, 104/1555; and 6.1%, 95/1555, respectively).

Details concerning concurrent drugs and conditions favouring QT prolongation, TdP and VA are shown in *Table 3*. Most reports 1381/1602 (86%) had no concomitant drugs at known risk of TdP on top of the culprit anticancer drug in the diLQT and/or TdP patients. Among these 1602 reports, the most reported drug classes with molecules concomitantly used at known risk of TdP were proton pomp inhibitors (8.6%; $n = 137$), antiemetics (7.4%, $n = 119$), anti-infectious agents (7.1%, $n = 114$), and antidepressants (6%, $n = 96$). Reports of concurrent conditions favouring diLQT and VA were frequent with 12% (275/2301) of infection, or cardiac conditions including 10% (239/2301) of heart failure and 8% (183/2301) of cardiac ischaemia (*Table 3*).

The median time to onset (in days) was not significantly different between patients with diLQT without TdP, TdP, and non-TdP VA (21 [IQR 7–91] vs. 23 [IQR 5·5–139] vs. 24 [IQR 4–120] days, respectively; $P = 0·93$) (*Figure 3*). When comparing different drug classes, the median time to onset was variable ranging from 9 days [IQR 3–23] for IT, 9 [IQR 3–34] for CT, 12 [IQR 3–38] for Misc treatments, 31 [IQR 11–140] for KI, to 142 [IQR 25–409] for HT ($P < 0.0001$). The differences between anticancer drug classes are displayed in *Figure 3*. The differences between anticancer drug molecules are displayed in Supplementary material online, *Table S4*.

Concordance of cardiac arrhythmia risk evaluations between VigiBase, CredibleMeds, and FDA

A total of 663 anticancer drugs were referenced in VigiBase (through 1 July 2019), of which 199 were FDA approved at least once and 195 currently approved (through 1 July 2019). Concordance between VigiBase results and data concerning diLQT, TdP, and/or VA available in CredibleMeds database (which aggregates all known drugs prolonging QT) or US FDA labels were moderate ($\kappa = 0.47$ [0.34–0.6], $P < 0.0001$ and 0.40 [0.27–0.54], $P < 0.0001$, respectively, Supplementary material online, *Figure S4*). Corresponding concordance between CredibleMeds and US FDA labels was high ($\kappa = 0.74$ [0.62–0.85], $P < 0.0001$). Twenty-three drugs (16 for diLQT or TdP and 14 for VA) were not described in CredibleMeds and/or FDA databases. In contrast, CredibleMeds

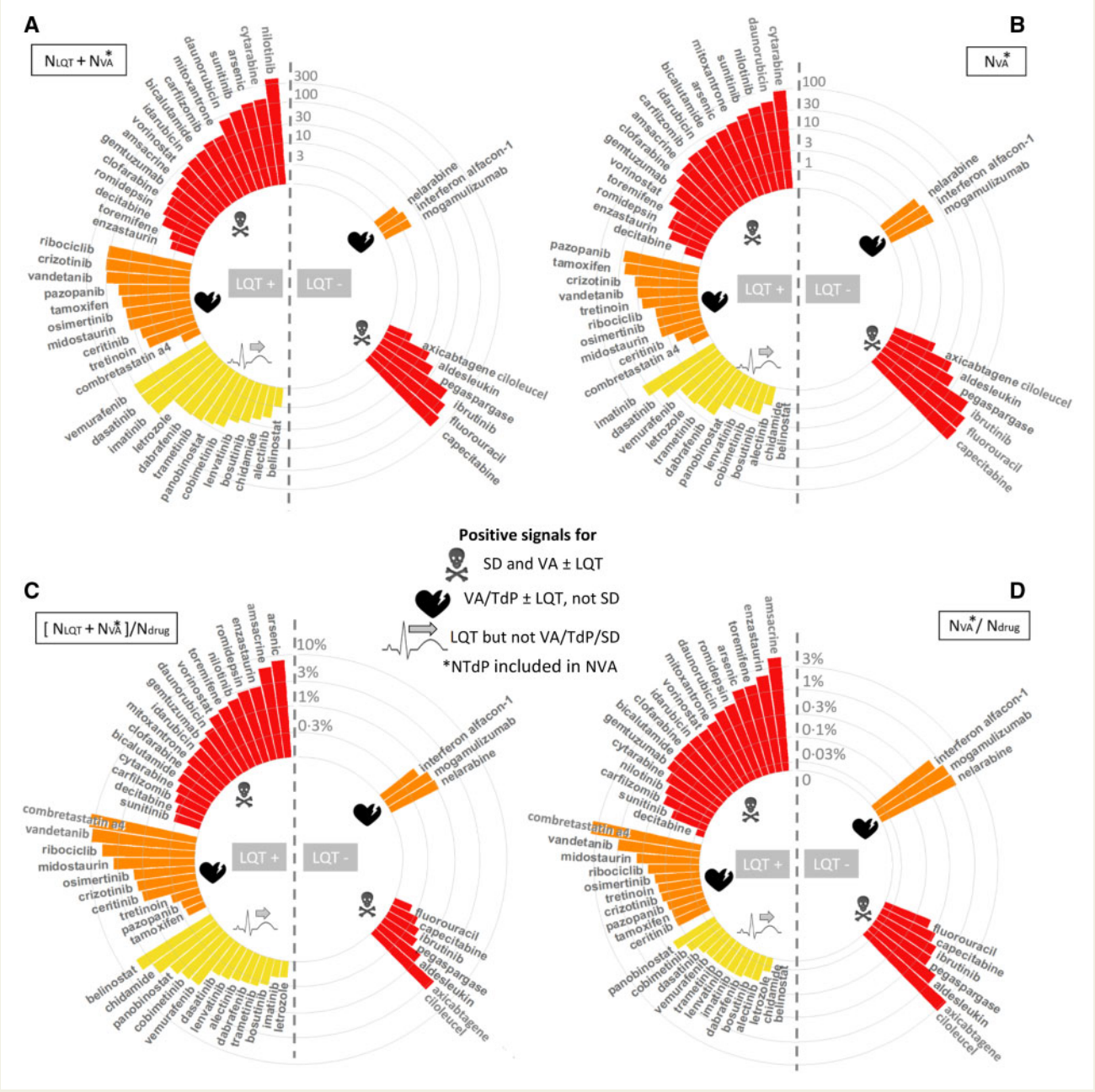


Figure 2 Three-level sudden death risk stratification for the 49 liable anticancer drugs associated with isolated drug-induced long QT (low risk), ventricular arrhythmias without sudden death (moderate risk), and ventricular arrhythmias with sudden death (high risk) identified in VigiBase (through 1 January 2019). Absolute number of ventricular arrhythmias (N_{VA}) including torsade de pointes (associated ($N_{LQT} + N_{VA}$) or not with diLQT reports by drug and sudden death risk level is displayed in (*A*) and (*B*), respectively. The corresponding proportion of such cases (N_{VA} or $N_{LQT} + N_{VA}$) over the total number of overall adverse drug reactions per drug (N_{drug}) are displayed in (*C*) and (*D*), respectively.

and/or FDA databases described 24 drugs associated with these ADR, which yielded no significant association in VigiBase. Details concerning the concordance per drug and specific type of cardiac arrhythmia (diLQT, TdP, VA) between these databases are presented in *Table 4*. Analyses of concordance restricted to the 199 FDA-approved drugs showed similar results (Supplementary material online, *Figure S4*). The most relevant new signals were those carrying a very high proportion of single suspect culprit drug (SSCD) in the reports (not confounded by the concurrent intake of other liable anticancer drugs) (Supplementary material online, *Table S4*). Within FDA-approved drugs, these latter were carfilzomib ($n = 19$, SSCD = 100%, proteasome inhibitor), imatinib ($n = 64$, SSCD = 73%, KI), alectinib ($n = 5$, SSCD = 100%, KI), axicabtagene-ciloleucel ($n = 4$, SSCD = 100%, CAR-T anti-CD19),

Table 3 Characteristics of patients receiving at least one of the 49 anticancer drugs associated significantly with drug-induced long QT syndrome, torsade de pointes, or ventricular arrhythmias through 01 January 2019, in VigiBase

	Total *N* = 2301
Age at **o**nset (years), median [IQR]	63 [51–71]
	N = 1609 available
Time to onset (days), median [IQR]	25 [7–97]
	N = 776 available
Reporting **y**ear	
1973–1993	22/2301 (1.0%)
1994–1998	34/2301 (1.5%)
1999–2003	67/2301 (2.9%)
2004–2008	191/2301 (8.3%)
2009–2013	553/2301 (24%)
2014–2018	1434/2301 (62.3%)
Notifier	
Healthcare professionals	1701/1943 (88%)
Non-healthcare professionals	242/1943 (12%)
Country of reporting	
Africa	1/2301 (0.1%)
Americas	1038/2301 (45.1%)
Asia	423/2301 (18.4%)
Europe	762/2301 (33.1%)
Oceania	77/2301 (3.3%)
Sex	
Female	931/2023 (46%)
Male	1092/2023 (54%)
Type of report	
diLQT without TdP; % including SD	1406/2301 (61%); 0/1406 (0%)
TdP; % including SD	196/2301 (9%); 44/196 (29%)
VA (not TdP); % including SD	699/2301 (30%); 184/699 (26%)
Seriousness	
Serious	1946/2078 (94%)
Death	317/2301 (14%)
SD	228/2301 (10%)
Number of anticancer drug suspected/interacting	
1	1793/2301 (78%)
2	313/2301 (14%)
≥3	195/2301 (8%)
Type of anticancer drugs suspected/interacting	
At least one cytotoxic	621/2301 (27%)
At least one hormonotherapy	138/2301 (6%)
At least one immunotherapy	33/2301 (1.4%)
At least one kinase inhibitor	1477/2301 (64.2%)
At least one miscellaneous drug	300/2301 (13%)
2 types or more combined	258/2301 (11.2%)
Indications	
Chronic myeloid leukaemia (CML)	363/1555 (23%)
Leukaemia other than CML	272/1555 (17%)
Colorectal cancer	126/1555 (8.1%)
Lung cancer	114/1555 (7.3%)
Breast cancer	104/1555 (6.7%)
Kidney cancer	95/1555 (6.1%)
Melanoma	90/1555 (5.8%)
Thyroid cancer	76/1555 (4.9%)
Myeloma	50/1555 (3.2%)
Lymphoma	47/1555 (3%)
Prostate cancer	24/1555 (1.5%)
Cancer other	90/1555 (5.8%)
Cancer no precision	52/1555 (3.3%)
Other hematological diseases or malignancies	34/1555 (2.2%)
Indication other than malignancy (inflammatory or autoimmune diseases)	18/1555 (1.2%)
Concurrent reported drugs at known risk of TdP (in the diLQT and/or TdP reports, *n* = 1602)	
0	1381/1602 (86.2%)
1	192/1602 (12%)
2	18/1602 (1.1%)
≥3	11/1602 (0.7%)
Concurrent reported drugs at conditional, possible or known risk of TdP(in the diLQT and/or TdP reports, *n* = 1602)	
0	1157/1602 (72.2%)
1	244/1602 (15.2%)
2	103/1602 (6.4%)
≥3	98/1602 (6.1%)
Classes of concurrently reported drugs at conditional, possible or known risk of TdP(in the diLQT and/or TdP reports, *n* = 1602)	
Anti-alpha1-adrenergics	3/1602 (0.2%)
Antiarrhythmic	41/1602 (2.6%)
Antidepressant	96/1602 (6.0%)
Antiemetic	119/1602 (7.4%)
Antihistamine	36/1602 (2.2%)
Anti-infectious	114/1602 (7.1%)
Antipsychotic	23/1602 (1.4%)
Diuretic-potassium lowering agents	96/1602 (6.0%)
Opioid	73/1602 (4.6%)
Proton pump inhibitor	137/1602 (8.6%)
Other cardiovascular drugs	2/1602 (0.1%)
Others	13/1602 (0.8%)
Concurrent reported condition favouring LQT/TdP or VA	
None	1216/2301 (53%)
Hypokalemia	107/2301 (4.7%)
Hypocalcemia	65/2301 (2.8%)
Hypomagnesemia	33/2301 (1.4%)
Diabetes mellitus	39/2301 (1.7%)
Uncontrolled hypertension	92/2301 (4%)
Pericarditis or pericardia effusion	25/2301 (1.1%)
Cardiac ischaemia	183/2301 (8%)
Heart failure	239/2301 (10%)

Continued

Table 3 *Continued*

	Total *N* = 2301
Bradycardia	94/2301 (4.1%)
Tachycardia	113/2301 (4.9%)
Conductive disorders	174/2301 (7.6%)
Atrial fibrillation	126/2301 (5.5%)
Hypotension or shock	134/2301 (5.8%)
Ischaemia or thrombosis (not cardiac nor cerebral)	75/2301 (3.3%)
Acute kidney injury	133/2301 (5.8%)
Acute hepatic injury	139/2301 (6%)
Acute stroke	43/2301 (1.9%)
Epilepsy	43/2301 (1.9%)
Infection (virus, bacteria, fungus, or parasite)	275/2301 (12%)
Inflammation	160/2301 (7%)
Other cardiovascular disorders	132/2301 (5.7%)

diLQT, drug-induced long QT syndrome; SD, sudden death; TdP, torsade de pointes; VA, ventricular arrhythmia.

mogamulizumab ($n = 5$, SSCD = 100%, C-C chemokine receptor type 4 inhibitor), and bicalutamide ($n = 30$, SSCD = 93%, androgen receptor antagonist). Interestingly, four drugs were flagged before any FDA approval (amsacrine [CT], combretastatin a4 [CT], chidamide [histone deacetylase inhibitor], and enzastaurin [KI]).

Discussion

In this worldwide pharmacovigilance study that included almost 19 million reports, disproportionality analyses yielded significant association between 49 anticancer drugs and cardiac arrhythmias, including diLQT, TdP, and VA. This detailed report summarizes all available data addressing drug-induced cardiac arrhythmias extracted from US FDA labels, CredibleMeds and VigiBase. We believe our data can serve as a compendium for all clinicians using anticancer drugs and considering their potential arrhythmic risk (*Table 4*). FDA labels mainly summarize data systematically gathered and analysed during drug development (thorough and concentration QT studies, clinical trials), and in some cases updates arising from post-marketing evaluation. Consensus achieved by experts from academia of these available data is found in the widely recognized CredibleMeds website for TdP risk.[31] VigiBase is a complementary source, which assembles data from real-life surveillance with spontaneous post-marketing reporting mainly arising from healthcare professionals. VigiBase has previously been utilized to describe other cardiovascular sequelae from anticancer therapies and has allowed a better appreciation of the magnitude of these toxicities.[5,7,10] Interestingly, in our work, 23 drugs represented new signals, while 24 flagged by Crediblemeds or FDA had no signal in VigiBase. These findings may guide clinicians and regulatory institutions to conduct further research to re-evaluate cardiac monitoring requirements focusing on these specific drugs. Moreover, information generally contained in FDA labels focus on the magnitude of QT prolongation identified in QT studies but does not provide information concerning VA and TdP risk as such, because these events are often too rare and not adjudicated in cancer-focused clinical trials. CredibleMeds website only assesses TdP risk in the context of QTc prolongation. Herein, we were able to identify three levels of SD risk profile with anticancer drugs only associated with isolated long QT (low risk), associated with VA without SD (moderate risk), and VA with SD (high risk). This SD risk stratification may prove useful to clinicians when confronted to difficulties in the risk/benefit assessment of pursuing a liable anticancer drug with a possible overall benefit for the patient. Importantly, we have identified a novel group that has not been particularly well flagged previously: drugs associated with potentially fatal VA but not mediated by QTc prolongation. This group is important to recognize in clinical situations where arrhythmias are suspected with a normal QTc on ECG. Lastly, this work provides a quantitative magnitude of disproportional association of 663 anticancer drugs with diLQT, TdP, and VA. These data may prove useful for translational cardio-oncology researches seeking at identifying new pathways involved in arrhythmias, as we recently showed with ibrutinib and identification of kinase-dependent off-target inhibition leading to atrial fibrillation.[16]

To date, this study is the most extensive, analysing over 42 000 suspected drug-induced cardiac arrhythmia events internationally reported from healthcare professionals. The evolution of reporting in VigiBase has been marked in the last decade by the introduction of new drug classes, KI, and IT; they currently represent the majority of reported drug-induced cardiac arrhythmias. As expected, CT have been associated with these ADR for far longer. In VigiBase, the first treatment to yield a significant association with cardiac arrhythmias was an anthracycline, idarubicin, in 1995. Of note, an average QTc >500 ms (normal <450 ms for men and <460 ms for women) or a >60-ms QTc change from baseline is considered as of particular concern (grade 3) according to the Common Terminology Criteria for Adverse Events, the grading mostly used in oncology trials. Anthracycline-related increase in QTc >60 ms vs. baseline has been reported with an incidence up to 14% with doxorubicin, and relates to their propensity to induce cardiomyocyte injury via overproduction of free radicals and alteration of cardiac ion currents, notably via I_{Ks} channel blockade and intra-cellular calcium dysregulation.[3,6,17] Our study also supports multiple observations previously reported in the literature, highlighting the robustness of the methodology with positive controls (e.g. arsenic trioxide, nilotinib, vandetanib, vorinostat, ribociclib).[6,17–19] The anticancer drug most reported with long QT in VigiBase was arsenic trioxide, a drug used against some leukaemia, and significantly associated with long QT/TdP since 2002 in VigiBase. The most comprehensive QT study included 99 patients with advanced malignancies who received 170 courses of arsenic trioxide. Of them, 35/99 (35.4%) developed increase in QTc >60 ms vs. baseline, and one developed asymptomatic TdP.[18] Nilotinib, a second-generation BCR-ABL inhibitor, has been previously linked to moderate increase in QTc (average QTc prolongation of 5–15 ms).[6] In studies, 2.5–4% of patients exhibited QTc prolongation >60 ms on nilotinib, and in one study, 1.2% of patients showed QTc >500 ms.[6,17,20] Similarly, vandetanib, a vascular endothelial growth factor receptor inhibitor, has been associated with long QT in a meta-analysis including nine phase II–III trials, which found a significant risk of QTc prolongation (all-grade according to the National Cancer Institute Common Toxicity Criteria v.2.0 or 3.0), 123/2552 (4.82%)

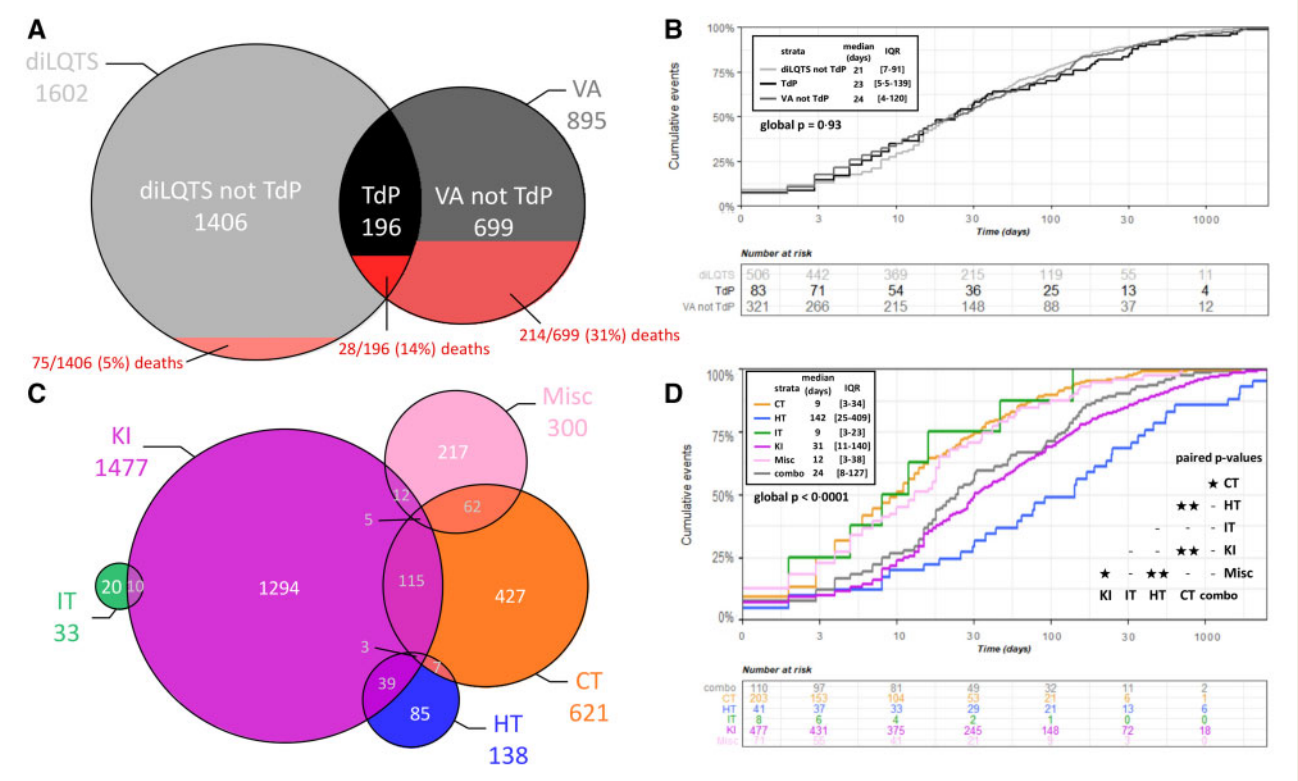


Figure 3 Overlap and overall fatality rate of drug-induced long QT syndrome, torsade de pointe, and ventricular arrhythmia reports associated with the 49 drugs identified in VigiBase (*A*) with their respective time to onset (*B*). Overlap in VigiBase for reports of drug-induced long QT and ventricular arrhythmia including torsade de pointes for these 49 drugs as a function of the underlying drug classes (*C*) with their corresponding time to onset (*D*). Differences in median time to onset by groups were compared by Wilcoxon tests and Dunn's post-test. * and ** stands for $P \leq 0.05$ and ≤ 0.0001, respectively. combo, reports containing at least one culprit anticancer drugs from at least two different anticancer drug classes; CT, cytotoxic therapy; HT, hormone therapy; IT, immunotherapy; KI, kinase inhibitor; Misc, miscellaneous.

in treated patients vs. 6/2204 (0.27%) in control group (relative-risk 7.90, $CI_{95\%}$ [4.03–15.50]).[21] Vorinostat, a histone deacetylase inhibitor used in the treatment of cutaneous T-cell lymphoma, was associated with QTc prolongation (>470 ms or delta >60 ms from baseline) in 5/116 (4.3%) patients in a retrospective review including phase I–II trials.[22] Ribociclib, a CDK 4/6 inhibitor used in breast cancer, was associated with QTc prolongation (>480 ms) in 11/334 (3.3%) of ribociclib-treated patients vs. 1/334 (0.3%) in the placebo arm, in its landmark randomized controlled trial.[23]

Distinct from drugs prolonging QT, several drugs were associated with VA without long QT. They included ibrutinib, and CAR-T. Indeed, although ibrutinib has not been associated with long QT (studies reported concentration-dependent QTc shortening),[24] it has been associated with atrial and VA and SD.[10,25] As described previously, it may correspond to a short-coupled variant of polymorphic ventricular tachycardia, which is thought to involve alteration in cardiac sarcoplasmic reticulum Ca^{2+} homeostasis associated with cardiac ryanodine receptor-calmodulin-dependent protein kinase pathways.[10,25] In our study, which found a few cases of CAR-T (axicabtagene-ciloleucel) related VA, there was also a signal towards association with VA but not long QT. In a retrospective study, 54% of tested patients who received CAR-T showed myocardial injury with troponin elevation and 12% developed a cardiac ADR (including heart failure, arrhythmias, and cardiac deaths).[26]

Our study also yielded new signals requiring further investigations to confirm the causality of the association, its magnitude and mechanisms at play. Alectinib, an ALK inhibitor, was not previously associated with VA nor QT modification, but it was associated with mild sinus bradycardia.[27] Carfilzomib, a proteasome inhibitor approved for the treatment of multiple myeloma, was known for its risk of cardiac failure, but not long QT and SD.[28] We also found imatinib associated with long QT, while imatinib was considered so far as relatively safe from a cardiovascular standpoint, as compared to other BCR-ABL inhibitors including nilotinib, ponatinib, and dasatinib.[6,17,29] In our study, a key element strengthening the association between these drugs and cardiac arrhythmias is the fact that in most reports alectinib (100%), carfilzomib (100%), and imatinib (73.4%) was the only anticancer drug suspect involved in the appearance of these cardiac ADR. Notably, we also observed hormone therapies blocking testosterone association with long QT and TdP, such as bicalutamide, an androgen receptor antagonist used in prostate cancer. In a translational study combining pharmacoepidemiological and mechanistic studies using iPSC cardiomyocytes, we recently confirmed the causal association between androgen deprivation and long QT and TdP.[7]

Table 4 Comparison of VigiBase signals (IC_{025} >0 vs. full database; or rOR_{025} >1 vs. anticancer drug background) for drug-induced long QT, torsade de pointes, and ventricular arrhythmias with information retrieved in CredibleMeds® website and US Food and Drug Administration labels (through 1 July 2019)

Drug	Signal in VigiBase				CredibleMeds TdP risk[a]	Signal in FDA label				New signal
	diLQT	TdP	VA	SD		diLQT	TdP	VA	SD	
Abarelix					Possible	In text				
Aldesleukin			Yes	Yes				BW		
Alectinib	Yes									Yes
Amsacrine	Yes	Yes	Yes	Yes		NA	NA	NA	NA	Yes
Apalutamide					Possible	In text				
Arsenic trioxide	Yes	Yes	Yes	Yes	Known	BW	BW	BW	BW	
Axicabtagene ciloleucel			Yes	Yes						Yes
Belinostat	Yes									Yes
Bendamustine					Possible					
Bicalutamide	Yes	Yes	Yes							Yes
Bortezomib				Yes	Possible	In text				
Bosutinib	Yes				Possible					
Cabozantinib					Possible					
Capecitabine			Yes	Yes	Possible					
Carfilzomib	Yes		Yes	Yes						Yes
Ceritinib	Yes	Yes			Possible	Warning	In text	In text	In text	
Chidamide	Yes					NA	NA	NA	NA	Yes
Clofarabine	Yes	Yes	Yes	Yes						Yes
Cobimetinib	Yes				Possible					
Combretastatin a4	Yes	Yes	Yes			NA	NA	NA	NA	Yes
Crizotinib	Yes	Yes			Possible	Warning				
Cyclophosphamide				Yes				In text		
Cytarabine	Yes	Yes	Yes	Yes						Yes
Dabrafenib	Yes				Possible					
Dasatinib	Yes				Possible	Warning				
Daunorubicin	Yes	Yes	Yes	Yes						Yes
Decitabine	Yes			Yes						Yes
Degarelix					Possible	Warning				
Encorafenib					Possible	Warning				
Enzastaurin	Yes		Yes	Yes		NA	NA	NA	NA	Yes
Epirubicin					Possible					
Eribulin					Possible	Warning				
Fluorouracil			Yes	Yes	Possible					
Gemtuzumab ozogamicin	Yes	Yes	Yes	Yes		In text				Yes
Gilteritinib					Possible	Warning				
Glasdegib					Possible	Warning		In text		
Goserelin						Warning				
Histrelin						Warning		In text	Warning	
Ibrutinib			Yes	Yes				Warning		
Idarubicin	Yes	Yes	Yes	Yes						Yes
Ifosfamide								Warning		
Imatinib	Yes									Yes
Inotuzumab					Possible	Warning				
Interferon alfacon-1			Yes					In text		
Ivosidenib					Possible	Warning		In text		
Lapatinib					Possible	Warning		In text		
Lenvatinib	Yes				Possible	Warning				
Letrozole	Yes									Yes
Leuprorelin					Possible	Warning			Warning	

Continued

Table 4 *Continued*

Drug	Signal in VigiBase				CredibleMeds TdP risk[a]	Signal in FDA label				New signal
	diLQT	TdP	VA	SD		diLQT	TdP	VA	SD	
Midostaurin	Yes	Yes	Yes		Possible	In text				
Mitoxantrone	Yes	Yes	Yes	Yes						Yes
Mogamulizumab			Yes							Yes
Necitumumab					Possible					
Nelarabine			Yes							Yes
Nilotinib	Yes	Yes	Yes	Yes	Possible	BW			BW	
Osimertinib	Yes	Yes			Possible	Warning				
Oxaliplatin				Yes	Known	In text	In text	In text		
Panobinostat	Yes				Possible	Warning				
Pazopanib	Yes	Yes			Possible	Warning	Warning		In text	
Pegaspargase			Yes	Yes						Yes
Ribociclib	Yes	Yes			Possible	Warning				
Romidepsin	Yes	Yes	Yes	Yes	Possible	Warning				
Sorafenib					Possible	Warning		In text		
Sunitinib	Yes	Yes		Yes	Possible	Warning	Warning	In text		
Tamoxifen	Yes	Yes			Possible					
Tipiracil-trifluridine					Possible					
Toremifene	Yes	Yes	Yes	Yes	Possible	BW	BW	BW		
Trametinib	Yes									Yes
Tretinoin	Yes	Yes								Yes
Triptorelin						Warning			Warning	
Vandetanib	Yes	Yes	Yes		Known	BW	BW	In text	BW	
Vemurafenib	Yes				Possible	Warning	In text	In text		
Vorinostat	Yes	Yes	Yes	Yes	Possible					

Among the 663 anticancer drugs screened (full list in Supplementary material online, *Table S3*), only those with evidence of association with diLQT, TdP, and VA mentioned in one of these three reference sources are shown. For these latter drugs, information concerning SD is also represented.
BW, box warning; diLQT, drug-induced long QT syndrome; FDA, Food and Drug Administration; NA: Not available; SD, sudden death; TdP, torsade de pointes; VA, ventricular arrhythmias.
[a]Signals accounted when drugs were flagged at possible or known risk for TdP (conditional risk not accounted).

Interestingly, our analysis showed that in four instances, signals of association between an incriminated drug under development and long QT, VA, and TdP, in VigiBase appeared prior to FDA approval of those drugs (namely, amsacrine, chidamide, combretastatin a4, and enzastaurin). In the specific field of drug-induced QT prolongation and cardiac arrhythmias, the agreement between the FDA labels, CredibleMeds, and VigiBase remains modest at best and emphasizes the complementarity of a multimodal approach to apprehend the toxicity of a specific drug.

The variety of anticancer drug classes associated with long QT highlights the heterogeneity of the mechanisms, which may underlie cardiac arrhythmias related to these agents. The generally accepted common mechanism whereby drugs prolong QT is a block of a key cardiac repolarizing potassium current, IKr.[8] While some anticancer drugs associated with diLQT and TdP have been shown to inhibit IKr, recent works focusing on anticancer drugs prolonging QT identified new pathways.[8] The *in vitro* effects of some KI to prolong cardiac action potentials (the cellular correlate of QT) can be rescued by intracellular phosphatidylinositol 3,4,5-trisphosphate, the downstream effector of phosphoinositide-3-kinase. This finding supports a role for inhibition of this enzyme, either directly or by inhibition of upstream kinases, to prolong QTc through mechanisms that are being investigated but include enhanced inward 'late' sodium current (INaL) activation during the plateau of the action potential.[8] These observations emphasize the need to better explore the kinome in general, and in particular, the effects of kinases located up- and downstream to that of phosphoinositide-3-kinase, to better understand their influence on cardiac electrophysiology.[30]

We acknowledge several inherent limitations to our results related to pharmacovigilance studies.[12] First, the exact denominator of patients exposed to anticancer drugs cannot be evaluated; hence, the true incidence of the events cannot be computed, and all values are expressed as relative to each other, with the basis that VigiBase aggregates millions of reports, and hence may allow for a generalization of the findings. The second bias stems from the observational and declarative nature of the reports with variable degree of exhaustivity. Third, the number of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions, and other bias.[12] Fourth, some drugs specifically annotated in Supplementary material online, *Table S4* (low SSCD) were systematically used in association, which require cautious interpretation of the results when one of these were known to be associated with cardiac arrhythmias (i.e letrozole, often asssociated with ribociclib with ribociclib being a well indentified liable

drug). Finally, in the specific context of anticancer drugs, the added risk due to these drugs is difficult to assess, as end-stage cancers may be associated with cardiac arrhythmias; however, this has been partially mitigated by our sensitivity disproportionality analysis restricted to patients on anticancer drugs. While these limitations are numerous, the added value of pharmacovigilance studies has already been demonstrated in various settings.[5,10,14,15] Nevertheless, they are only to be taken as signal-generating studies and all hypotheses generated require validation by translational mechanistic or prospective studies.[7,10] Indeed, while randomized clinical trials are mandatory to establish efficacy, their power to detect ADR may be lower, due to the rarer incidence in these events and the fact that 'real-world population' may differ from included patients in the said clinical trial. Translational experimental studies specifically designed to answer a question of cardiotoxicity in oncology remain the most comprehensive design available, yet.[7,16]

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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The supplied data from VigiBase come from various sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of World Health Organization. We thank the custom searches team at the Uppsala Monitoring Centre (Uppsala, Sweden) research section, without whom this study would not have been possible.

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Author contributions

J.-E.S. and P.G. were involved in study design. P.G. did the literature search. P.G. and J.-E.S. made the figures. P.G., J.-E.S., and B.L.-V. were involved in data collection. P.G. and J.-E.S. analysed the data. P.G., L.S.N., and J.-E.S. were involved in data interpretation. P.G., L.S.N., J.-E.S., J.J.M., C.F.-B., S.E., A.C., D.R., and B.L.-V. were involved in the writing of the manuscript. All authors edited the manuscript.

Conflict of interest: J.-E.S. had paid lecture fees from AstraZeneca and BMS unrelated to this work and have patents pending and issued related to methods for detecting the risk of torsade de pointes. J.J.M. had consultancy fees from BMS, AstraZeneca, Deciphera, Janssen, Takeda, Cytokinetics, Audentes, Boston Biomedical, and Myovant unrelated to this work. All other authors have nothing to disclose.

Data availability

Data are available upon request to VigiBase (https://www.who-umc.org/vigibase/vigibase/).

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