ORIGINAL RESEARCH

Incidence of Cancer Treatment–Induced Arrhythmia Associated With Novel Targeted Chemotherapeutic Agents

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Background—The incidence of cancer treatment–induced arrhythmia (CTIA) associated with novel, targeted chemotherapeutic agents (TCAs) has not been well described.

Methods and Results—We identified all patients treated at our institution from January 2010 to December 2015 with selected TCAs. We defined CTIA as any new arrhythmia diagnosis code within 6 months after treatment initiation. As a comparison, we also identified patients treated with anthracycline chemotherapy during the same period. We identified 5026 patients, of whom 2951 (58.7%) received TCAs and 2075 (41.3%) received anthracycline chemotherapy. In the overall cohort, 601 patients (12.0%) developed CTIA. Patients with CTIA were significantly older and more likely to have hypertension, diabetes mellitus, congestive heart failure, coronary disease, and sleep apnea. The incidence of CTIA at 6 months was significantly lower in the TCA group (9.3% versus 15.8%; $P<0.001$). In multivariate analysis, a history of hypertension (hazard ratio, 1.63; 95% confidence interval, 1.34–1.98), congestive heart failure (hazard ratio, 2.12; 95% confidence interval, 1.78–2.68), and male sex (hazard ratio, 1.25; 95% confidence interval, 1.06–1.47) were associated with a significantly increased risk of CTIA, whereas treatment with TCAs, compared with anthracycline chemotherapy, was associated with a significantly lower risk (hazard ratio, 0.60; 95% confidence interval, 0.51–0.71).

Conclusions—Compared with anthracyclines, treatment with TCAs was associated with an ≈40% reduced risk of new-onset arrhythmia diagnoses during the first 6 months of treatment. **(*J Am Heart Assoc*. 2018;7:e010101. DOI: 10.1161/JAHA.118.010101)**

Key Words: arrhythmia • cancer treatment–induced arrhythmia • oncology

Traditional cancer therapies, such as anthracyclines and radiation therapy, have well-established cardiovascular toxicities. With improved understanding of molecular pathways, the past decade has seen a rapid expansion in availability of novel, targeted chemotherapeutic agents (TCAs) that are designed to specifically inhibit targets critical for oncogenesis. These novel agents have resulted in improved oncologic outcomes in many forms of cancer and have frequently been associated with improved adverse effect profiles in light of the more specific mechanisms of action. However, even among targeted agents, several important forms of cardiovascular toxicity have emerged, because of either off-target effects or on-target toxicities in circumstances in which the target of interest also plays a crucial role in the cardiovascular system.[1] For instance, symptomatic congestive heart failure (CHF) has a reported incidence of 2% to 4% in clinical trials of trastuzumab, a monoclonal antibody targeting the human epidermal growth factor receptor kinase, likely because of a previously unrecognized role for human epidermal growth factor receptor kinase in myocyte function, resulting in on-target toxicity. Similarly, drugs targeting the vascular endothelial growth factor pathway, such as the tyrosine kinase inhibitor (TKI) sunitinib, have been associated with putative on- and off-target toxicities, resulting in an increased risk of hypertension, thromboembolic complications, and cardiomyopathy.[1,2] Ibrutinib, another TKI used to treat hematologic malignancies, has demonstrated an association with the development of atrial fibrillation in clinical trials.[3]

Although arrhythmic complications have been reported in conjunction with TCAs, the overall incidence of and risk factors for the development of cancer treatment–induced arrhythmia (CTIA) associated with novel agents have not been

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Clinical Perspective

What Is New?

- In a large, retrospective cohort, the incidence of new arrhythmia diagnoses during the first 6 months of de novo chemotherapy was significantly lower with novel, targeted chemotherapeutic agents compared with anthracycline chemotherapy.
- Risk factors for cancer treatment–induced arrhythmia included hypertension, history of congestive heart failure, and male sex.
- Significant differences were noted in the incidence of cancer treatment–induced arrhythmia across classes of targeted chemotherapeutic agents.

What Are the Clinical Implications?

- The mechanisms by which different classes of targeted chemotherapeutic agents may be associated with differing levels of risk for cancer treatment–induced arrhythmia require further study.
- Methods for preventing cancer treatment–induced arrhythmia need to be evaluated.

well described. Therefore, we sought to describe the incidence of CTIA associated with novel TCAs and compared it with the incidence of CTIA associated with anthracycline chemotherapy (AC), given the well-established cardiovascular toxicity profile of this class of agents.[4,5]

Methods

The protocol for this study was approved by the Emory University Institutional Review Board, and the requirement for informed consent was waived. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. We performed a retrospective, electronic medical records (EMRs) query to identify all patients treated de novo at our institution in either the inpatient or the outpatient setting from January 2010 to December 2015. Inpatient and outpatient pharmacy orders were queried for the following TCAs: monoclonal antibodies targeting cell proliferation pathways (trastuzumab and bevacizumab), TKIs (ibrutinib, imatinib, sunitinib, vemurafenib, sorafenib, erlotinib, and lapatinib), and immune checkpoint inhibitors (nivolumab, pembrolizumab, ipilimumab, atezolizumab, and tremelimumab). Only patients who were treated with chemotherapeutic agents for the first time were included; those who had been previously treated at our institution with chemotherapy were excluded from this analysis. Patients who received multiple agents (either multiple TCAs or TCA+AC) in either an overlapping or a sequential manner during the period of interest were excluded. For patients who received bevacizumab, only those who received the drug via the intravenous route were included, to exclude those patients receiving the drug for ocular indications. The incidence of CTIA in patients treated with TCAs was compared with that in patients treated with AC during the same period. The anthracycline agents included were doxorubicin, daunorubicin, and epirubicin.

Clinical End Points

CTIA was defined as a new diagnosis of the following during the 6 months after the initiation of chemotherapy: atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, premature atrial and/or ventricular contractions, sinus node dysfunction, atrioventricular block, and unspecified forms of tachycardia. Additionally, patients who underwent pacemaker or defibrillator implantation or catheter ablation during this period were

Table 1. Baseline Characteristics

Characteristics	Targeted Agents (n=2951)	Anthracyclines (n=2075)	*P* Value
Age, y	59.1±13.8	55.3±13.99	<0.001
Male sex	1309 (44.4)	1099 (53.0)	<0.001
Body mass index, kg/m^2	27.3±6.3	28.3±6.7	<0.001
Hypertension	1664 (56.4)	1230 (59.3)	0.043
Diabetes mellitus	622 (21.1)	563 (27.1)	<0.001
Congestive heart failure	306 (10.4)	262 (12.6)	0.015
Coronary artery disease	704 (23.9)	494 (23.8)	0.973
History of coronary revascularization	188 (6.4)	109 (5.3)	0.101
Obstructive sleep apnea	155 (5.3)	130 (6.3)	0.137

Data are presented as mean±SD or number (percentage).

Table 2. Agents Included in the Targeted and Anthracycline Groups

Agents	Value
Targeted agents	
Bevacizumab	781 (26.5)
Nivolumab	51 (1.7)
Pembrolizumab	35 (1.2)
Ibrutinib	120 (4.1)
Imatinib	411 (13.9)
Ipilimumab	158 (5.4)
Erlotinib	411 (13.9)
Lapatinib	42 (1.4)
Sorafenib	213 (7.2)
Sunitinib	201 (6.8)
Trastuzumab	482 (16.3)
Vemurafenib	46 (1.6)
Total	2951
Anthracyclines	
Doxorubicin	1979 (95.4)
Epirubicin	47 (2.3)
Daunorubicin	49 (2.3)
Total	2075

Data are presented as number (percentage).

included in the definition of CTIA. Cases of CTIA were identified by searching our institutional EMR for the previously described diagnoses in either the medical problem list fields or the billing diagnoses fields. Only new arrhythmia diagnoses were included in the definition of CTIA. Patients who had any of the previously described diagnoses documented in the EMR before the initiation date of chemotherapy were presumed to have a preexisting arrhythmia and were excluded from this analysis. Baseline demographic data and clinical covariates known to be associated with the development of arrhythmias (hypertension, diabetes mellitus, CHF, coronary artery disease, history of coronary revascularization, and obstructive sleep apnea) were also ascertained by EMR query. Clinical covariates were present at the time of chemotherapy initiation, before the development of arrhythmia diagnoses. For each patient, the last documented clinical encounter within our institutional EMR was identified to determine the duration of follow-up.

Statistical Analysis

Continuous variables are presented as mean±SD, and categorical data are summarized as frequencies and percentages. Comparisons between groups were tested using the Fisher's exact test, χ^2 test, or *t* test, as appropriate. The primary end point for the analysis was the incidence of CTIA at 6 months, stratified by treatment group (TCA versus AC). The time course of the primary end point was estimated using Kaplan-Meier analysis and tested with the log-rank test. Cox regression models were performed to identify significant multivariable correlates of CTIA. Univariate predictors of CTIA with a $P<0.1$ were included in the multivariable analysis. Proportional hazards assumptions were verified by graphical analysis of Schoenfeld residuals. A 2-tailed $P<0.05$ was considered significant. All statistical analyses were performed using Statistica (Statsoft, Tulsa, OK).

Results

A total of 5026 patients were identified in the database query, of whom 2951 (58.7%) were treated with TCAs and 2075 (41.3%) were treated with AC. Baseline characteristics of the

Table 3. Baseline Characteristics Stratified by the Presence of CTIA

Characteristics	With CTIA (n=601)	Without CTIA (n=4425)	*P* Value
Age, y	59.3±14.5	57.3±13.9	0.001
Male sex	328 (54.6)	2080 (47.0)	<0.001
Body mass index, kg/m^2	27.5±6.6	27.8±6.5	0.322
Hypertension	438 (72.9)	2456 (55.5)	<0.001
Diabetes mellitus	179 (29.8)	1006 (22.7)	<0.001
Congestive heart failure	140 (23.3)	428 (9.7)	<0.001
Coronary artery disease	194 (32.3)	1004 (22.7)	<0.001
History of coronary revascularization	46 (7.7)	251 (5.7)	0.065
Obstructive sleep apnea	50 (8.3)	235 (5.3)	0.005

Data are presented as mean±SD or number (percentage). CTIA indicates cancer treatment–induced arrhythmia.

treatment groups are presented in Table 1. Patients in the TCA cohort were significantly older, were more likely to be women, had a lower body mass index, and were less likely to be hypertensive, to be diabetic, or to have a history of CHF than those in the AC group. The number of patients treated with each specific agent in the TCA and AC groups is presented in Table 2. Bevacizumab was the most commonly prescribed TCA, accounting for just over a quarter of that cohort, whereas doxorubicin accounted for most patients treated with AC.

In the overall cohort, 601 patients (12.0%) developed CTIA. Table 3 presents characteristics of patients who did and did not develop CTIA. Those who developed arrhythmia diagnoses during treatment were older, were more likely to be men, and were more likely to have hypertension, diabetes mellitus, CHF, coronary artery disease, and obstructive sleep apnea than those who did not develop CTIA. In the TCA group, 273 patients (9.3%) developed CTIA compared with 328 patients (15.8%) in the AC group ($P<0.001$). The incidence of CTIA, stratified by treatment group, is presented in Figure 1. Predictors of CTIA in the TCA and AC groups are presented in Tables 4 and 5, respectively. In both groups, patients with CTIA were significantly more likely to have hypertension and CHF. In the TCA group (Table 4), those with CTIA were also older, were more likely to be men, and were more likely to have a history of coronary revascularization, but they were less likely to have diabetes mellitus. In the AC group (Table 5), those with CTIA were more likely to have diabetes mellitus, obstructive sleep apnea, and coronary artery disease but not necessarily coronary revascularization.

To identify significant multivariate predictors of CTIA, we performed a Cox model (n=5025) including treatment group (TCA versus AC) as a covariate. Results of the model are presented in Table 6. Male sex (hazard ratio, 1.251; 95% confidence interval, 1.061–1.474), hypertension (hazard ratio, 1.626; 95% confidence interval, 1.335–1.980), and CHF (hazard ratio, 2.188; 95% confidence interval, 1.783–2.681) were all associated with a significantly increased risk of CTIA. In contrast, treatment with a TCA (compared with AC) was associated with a significantly lower risk of CTIA (hazard ratio, 0.599; 95% confidence interval, 0.508–0.706).

A breakdown of the specific diagnoses and billing codes that led to the identification of CTIA is presented in Table 7. The diagnoses highlighted in red in the top panel in Table 7 were believed to be nonspecific and of unclear clinical relevance. Therefore, we performed a subanalysis in which the EMR was reviewed for each of the 392 patients with one of the nonspecific diagnoses to see if a specific diagnosis could be identified on the basis of more detailed medical record review, including ECGs, Holter/event monitors, and

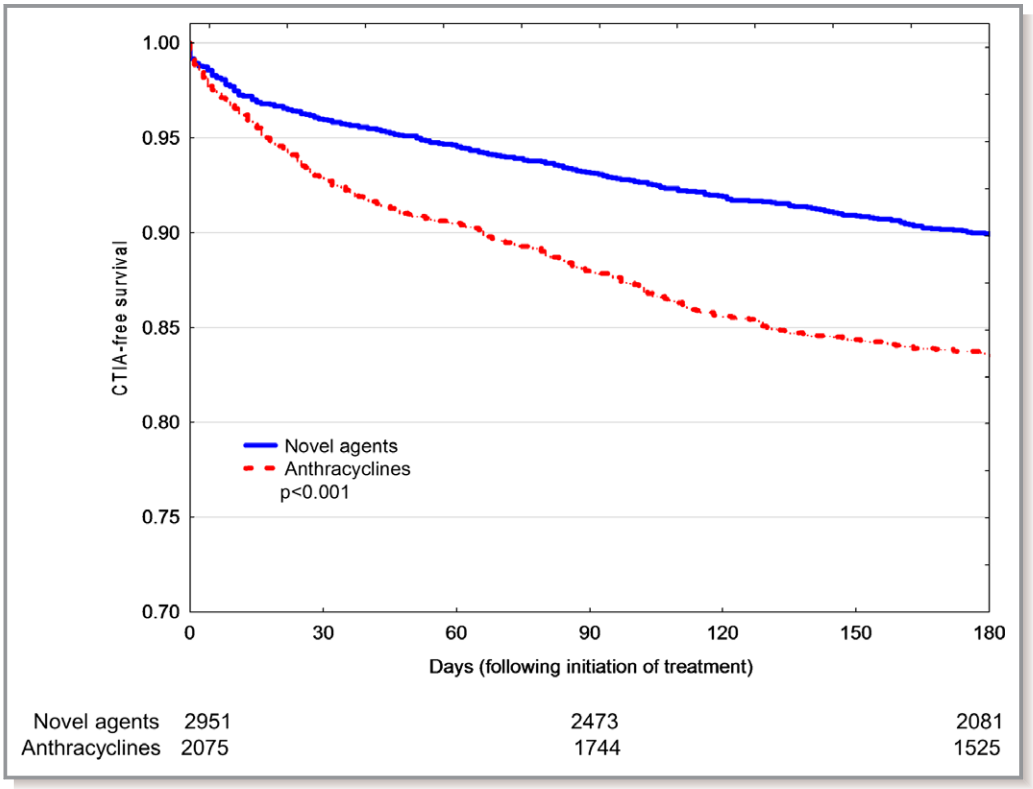

Figure 1. Kaplan-Meier incidence of cancer treatment–induced arrhythmia (CTIA), stratified by treatment group. Number at risk in each group is plotted beneath the figure.

Table 4. Targeted Treatment Group Stratified by the Presence of CTIA

Characteristics	With CTIA (n=273)	Without CTIA (n=2678)	*P* Value
Age, y	62.7±14.3	58.7±13.7	<0.001
Male sex	139 (50.9)	1170 (43.7)	0.025
Body mass index, kg/m^2	27.0±6.4	27.4±6.3	0.379
Hypertension	206 (75.5)	1458 (54.4)	<0.001
Diabetes mellitus	75 (14.3)	547 (20.4)	0.008
Congestive heart failure	67 (24.5)	239 (8.9)	<0.001
Coronary artery disease	94 (14.3)	610 (22.8)	<0.001
History of coronary revascularization	31 (11.4)	157 (5.9)	0.001
Obstructive sleep apnea	19 (7.0)	136 (5.1)	0.198

Data are presented as mean±SD or number (percentage). CTIA indicates cancer treatment–induced arrhythmia.

Table 5. Anthracycline Treatment Group Stratified by the Presence of CTIA

Characteristics	With CTIA (n=328)	Without CTIA (n=1747)	*P* Value
Age, y	56.5±14.0	55.0±14.0	0.091
Male sex	189 (57.6)	910 (52.1)	0.071
Body mass index, kg/m^2	27.9±6.8	28.4±6.7	0.218
Hypertension	232 (70.7)	998 (57.1)	<0.001
Diabetes mellitus	104 (31.7)	459 (26.3)	0.050
Congestive heart failure	73 (22.3)	189 (10.8)	<0.001
Coronary artery disease	100 (30.5)	394 (22.6)	0.002
History of coronary revascularization	15 (4.6)	94 (5.4)	0.685
Obstructive sleep apnea	31 (9.5)	99 (5.7)	0.013

Data are presented as mean±SD or number (percentage). CTIA indicates cancer treatment–induced arrhythmia.

Table 6. Multivariate Predictors of CTIA (n=5025)

Predictor	Hazard Ratio	95% Confidence Interval	*P* Value
Age*	1.006	0.999–1.013	0.073
Male sex	1.251	1.061–1.474	0.008
Targeted agent†	0.599	0.508–0.706	<0.001
Hypertension	1.626	1.335–1.980	<0.001
Diabetes mellitus	0.962	0.797–1.160	0.682
Congestive heart failure	2.188	1.783–2.681	<0.001
Coronary artery disease	1.088	0.892–1.325	0.407
History of coronary revascularization	0.751	0.539–1.047	0.092
Obstructive sleep apnea	1.124	0.837–1.511	0.437

CTIA indicates cancer treatment–induced arrhythmia.
*Per year increase.
†Compared with treatment with anthracyclines.

clinical notes. If a more specific diagnosis could be identified on the basis of medical record review, the patient was reassigned to that specific diagnosis for the subanalysis. If only sinus rhythm (sinus bradycardia, sinus tachycardia, or normal sinus rhythm) was identified or no clear diagnosis was evident, those patients were considered not to have

Table 7. Distribution of Arrhythmia Diagnoses Among Patients With CTIA

Diagnosis	Targeted Agents (n=273)	Anthracyclines (n=328)
Atrial fibrillation	65	47
Atrial flutter	2	2
Paroxysmal ventricular tachycardia	8	12
Sinoatrial node dysfunction	14	16
Supraventricular premature beats	1	2
Ventricular flutter	0	1
Paroxysmal supraventricular tachycardia	17	22
Cardiac dysrhythmia, unspecified	58	79
Other premature beats	7	2
Other specified cardiac dysrhythmias	99	144
Paroxysmal tachycardia, unspecified	2	1
First-degree AV block	1	4
Second-degree AV block (Mobitz I)	1	0
Atrial fibrillation	6	7
Atrial flutter	1	0
Premature atrial contraction	10	14
Premature ventricular contraction	19	12
Sinoatrial node dysfunction	1	0
Sinus bradycardia	17	35
Sinus tachycardia	66	90
No diagnosis	5	14
Normal sinus rhythm	39	50

CTIA indicates cancer treatment–induced arrhythmia.

CTIA for the purpose of the subanalysis. The lower panel of Table 7 displays the diagnoses after review of individual patient medical records and reclassification. Therefore, in the subanalysis, we included only patients in whom a specific arrhythmia diagnosis could be identified. Using this approach, the incidence of specific arrhythmia diagnoses stratified by treatment group is presented in Figure 2. The incidence of specific arrhythmias was lower than the incidence of CTIA reported in the overall analysis (which included the nonspecific diagnoses). However, patients in the TCA cohort continued to have a significantly lower incidence of specific arrhythmias at 6 months after initiation of treatment, compared with those treated with AC (5.2% versus 7.4%; P=0.005).

Given prior data suggesting an association between certain TCAs and atrial arrhythmias, we performed an additional analysis looking only at the incidence of atrial fibrillation/atrial flutter during the 6 months after initiation of treatment. Results are presented in Figure 3. There was no significant difference in the incidence of atrial arrhythmias (TCA versus AC, 2.7% versus 3.1%; P=0.556).

We also performed exploratory analyses looking at the incidence of CTIA in specific subgroups of TCAs. In Figure 4, we grouped TCAs on the basis of the primary molecular target of action: bevacizumab, sorafenib, and sunitinib were grouped as primarily targeting vascular endothelial growth factor, erlotinib and lapatinib were grouped as targeting epidermal growth factor receptor, and nivolumab and pembrolizumab were grouped as targeting PD-1. The other agents were considered to have distinct targets and analyzed separately. This exploratory analysis was performed with the acknowledgment that some agents, in particular TKIs, may have multiple overlapping targets. Agents were grouped on the basis of the putative primary molecular target to determine whether agents targeting certain pathways may be more strongly associated with CTIA than others. As is evident from the figure, the incidence of CTIA was highest for vemurafenib, followed by ibrutinib and imatinib, with significant differences noted across groups. We also grouped TCAs on the basis of drug class (monoclonal antibodies, TKIs, and immune checkpoint inhibitors) to look for differences in CTIA incidence as a class effect. These results are presented in Figure 5. The incidence of CTIA at 6 months was significantly lower among patients treated with monoclonal antibodies (7.4%), compared with both TKIs (11.9%) and immune checkpoint inhibitors (13.0%; P<0.001). There was no significant difference in CTIA incidence between TKIs and immune checkpoint inhibitors.

Discussion

Our data demonstrate that ≈12% of patients treated with either TCAs or anthracyclines received a new arrhythmia diagnosis within the first 6 months of treatment. The incidence of CTIA was significantly greater among those with a history of cardiovascular comorbidities, such as hypertension and heart failure. In contrast, treatment with a novel TCA was associated with an ≈40% relative risk reduction in the incidence of CTIA compared with anthracycline chemotherapy. Among patients treated with targeted agents, TKIs and immune checkpoint inhibitors were associated with a higher incidence of CTIA than monoclonal antibodies.

Although several important cardiovascular toxicities have been associated with chemotherapeutic agents, the incidence and risk factors leading to the development of arrhythmias in the setting of chemotherapy, in particular with novel targeted agents, have not been well characterized. Available data suggest an increased risk of atrial arrhythmias during treatment with ibrutinib, possibly mediated by inhibition of

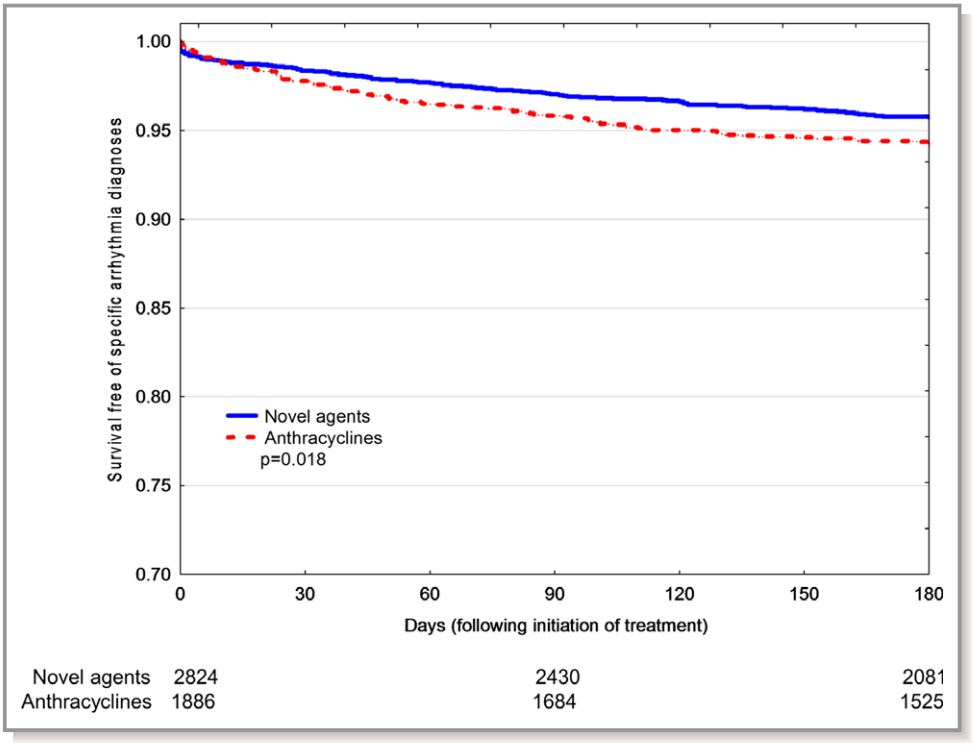

Figure 2. Incidence of specific arrhythmia diagnoses, stratified by treatment group. For this analysis, those patients without a specific arrhythmia diagnosis were considered arrhythmia free. Number at risk in each group is plotted beneath the figure.

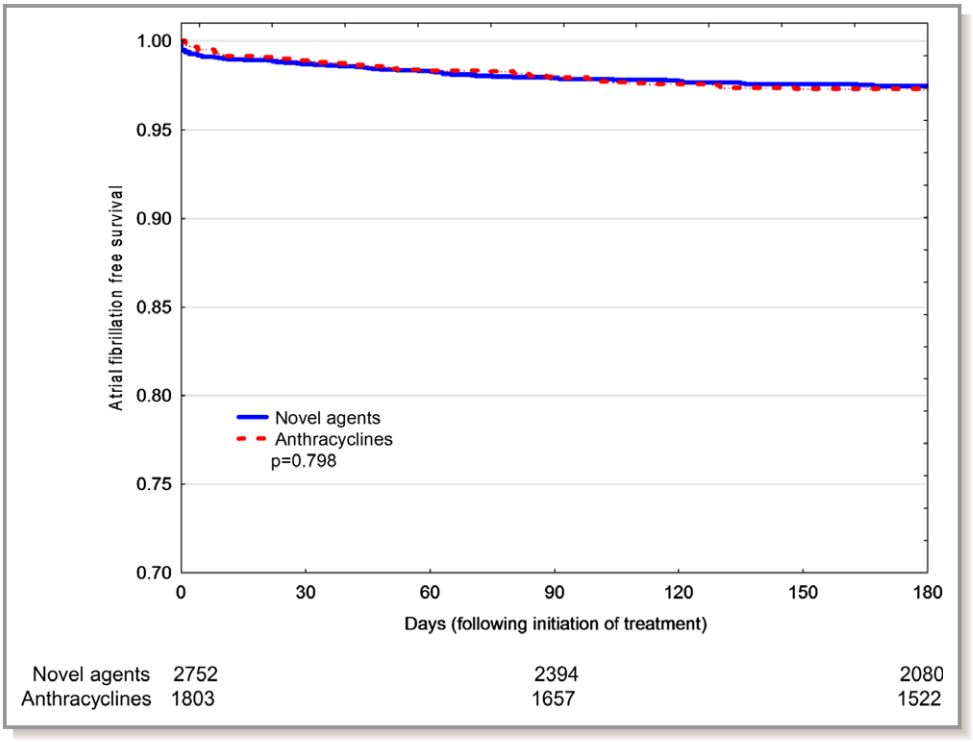

Figure 3. Incidence of atrial fibrillation/atrial flutter, stratified by treatment group. Number at risk in each group is plotted beneath the figure.

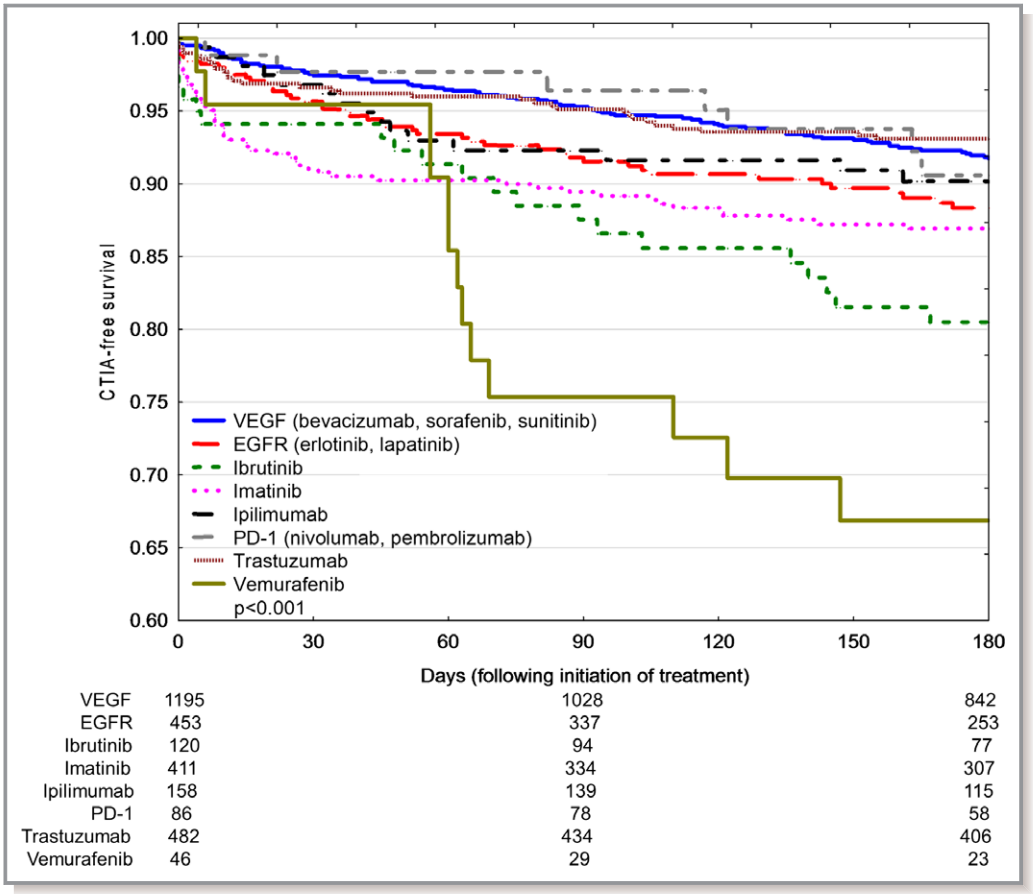

Figure 4. Kaplan-Meier incidence of cancer treatment–induced arrhythmia (CTIA), stratified by primary molecular target among novel agents. Number at risk in each group is plotted beneath the figure. EGFR indicates epidermal growth factor receptor; and VEGF, vascular endothelial growth factor.

the phosphatidylinositol 3-kinase–protein kinase B pathway, which plays a role in cardiomyocyte homeostasis.[6] Crizotinib has been associated with significant sinus bradycardia,[7] potentially via antagonism of sodium and L-type calcium channels.[8] In contrast to direct molecular effects, in other circumstances, chemotherapy may lead to arrhythmias via more generalized mechanisms, including myocardial damage leading to cardiomyopathy, systemic inflammation, and cytokine activation.[3] Trastuzumab has been associated with arrhythmias most commonly in the setting of underlying cardiomyopathy, with >5% of patients treated with this agent discontinuing therapy because of arrhythmias, primarily atrial fibrillation, in one cohort.[9] Newer immune checkpoint inhibitors, such as nivolumab and pembrolizumab, may have proinflammatory effects, resulting in both atrial and ventricular arrhythmias in the setting of myocarditis.[10,11]

Although associations between specific chemotherapeutic agents and arrhythmias have been described, relatively little data exist on the overall incidence of arrhythmias in the setting of chemotherapy. Our study reports one of the first assessments of CTIA incidence across a broad range of agents; on the basis of our definition, ≈12% of patients developed CTIA within 6 months of treatment with either TCAs or AC. Additionally, CTIA was significantly more common among patients with underlying cardiovascular comorbidities, suggesting that cancer itself, or treatment with chemotherapy, may unmask a propensity to arrhythmias among those who are already predisposed. The incidence was significantly higher among those treated with anthracyclines compared with those treated with novel, targeted agents. We chose to use anthracyclines as the comparator group given the well-established cardiovascular toxicity profile associated with this class of agents.[12,13] Although it is conceivable that TCAs, via more targeted molecular mechanisms, may result in lower rates of myocardial damage and off-target effects than anthracyclines, and therefore result in a lower incidence of arrhythmias, our data do not provide any specific support for the mechanism of difference in CTIA incidence between the 2 groups of agents. Among patients treated with TCAs, our data also suggest that TKIs and immune checkpoint inhibitors are associated with a significantly increased risk of CTIA compared with monoclonal antibodies.

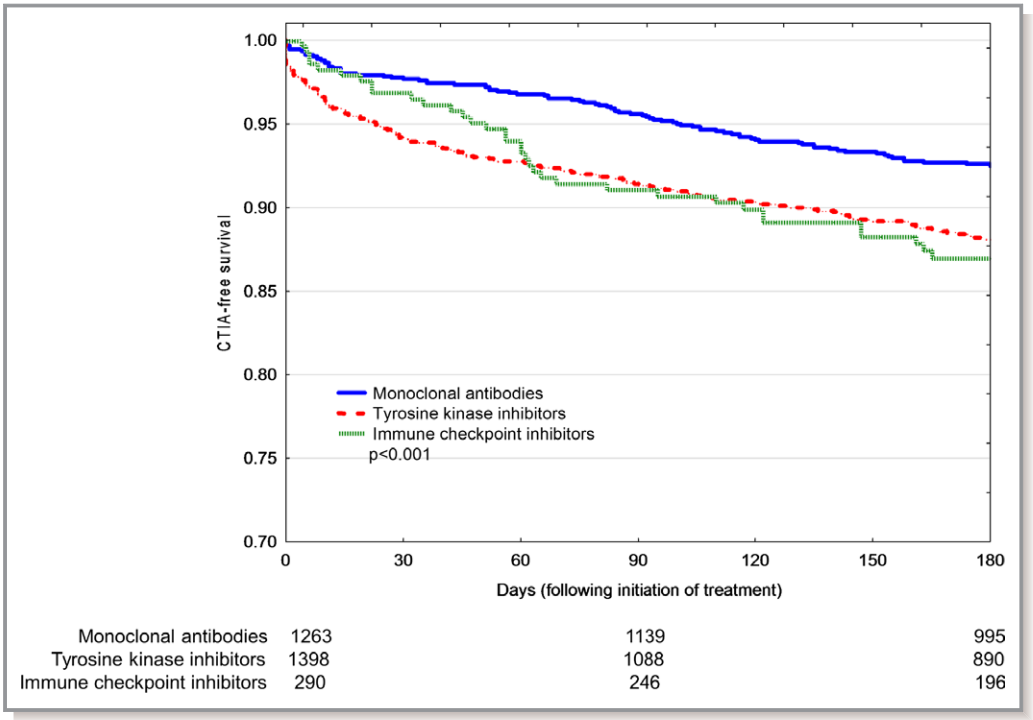

Figure 5. Kaplan-Meier incidence of cancer treatment–induced arrhythmia (CTIA), stratified by class of targeted agent. Number at risk in each group is plotted beneath the figure.

For the definition of CTIA used in our study, we chose to use a broad definition including some rhythms that may be considered benign and clinically insignificant. For instance, premature atrial and ventricular contractions have traditionally been considered to have little clinical significance. However, a sizeable body of literature has emerged recently that has identified even low burdens of atrial[14–16] and ventricular[14,16,17] ectopy as significant, independent predictors of numerous important end points, including overall survival,[15–17] sudden cardiac death,[14] heart failure,[16,17] and atrial fibrillation.[15,16] These associations even extend to ectopy picked up on a single 12-lead ECG.[16] Therefore, the occurrence of these seemingly benign rhythms may not be as innocuous as once assumed. Whether the occurrence of premature atrial and ventricular contractions in the setting of chemotherapy is associated with similar adverse long-term prognosis will require further study and is beyond the scope of our work. However, until these associations are better understood and the prognostic implications of these rhythms in the setting of chemotherapy is evaluated, we believe it is worthwhile to include them in the definition of CTIA.

Limitations

Several important limitations of our work should be noted. First, we do not have data on the specific forms of cancer or stage of cancer for which chemotherapy was prescribed. It is conceivable that differences in the underlying malignancy may contribute to the risk of CTIA noted between targeted agents and anthracyclines, or among specific categories of TCAs. Additionally, although CHF emerged as an important risk factor for CTIA, we do not have data on ejection fraction or severity of heart failure. We are also unable to comment on the incidence of significant electrolyte abnormalities or other metabolic perturbations, such as thyroid dysfunction, that may have occurred during chemotherapy and could have predisposed to arrhythmias. Furthermore, we do not have data on concomitant medications that may have interacted with chemotherapeutic agents and affected the incidence of CTIA. In terms of the definition of CTIA used in this analysis, we excluded patients with arrhythmia diagnoses before initiation of chemotherapy. However, as a tertiary referral center, it is possible that patients may have had prior arrhythmia diagnoses, preceding the initiation of chemotherapy, that were managed outside our healthcare system and, therefore, would not have been captured by our EMR query.

Given the large size of the cohort in this study, we used billing codes and medical problem lists to identify cases of CTIA. However, this included many nonspecific arrhythmia diagnosis codes of unclear clinical significance. We chose to include these nonspecific diagnoses in the primary analysis based, in part, on the idea that whatever arrhythmia was identified, it was believed to be significant enough to generate an entry in the medical problem list or a billing code and,

therefore, merited inclusion in the definition of CTIA. It is conceivable that some of these diagnoses may not have had significant clinical consequences. However, in the absence of a clear definition in the cardio-oncology literature for CTIA and which arrhythmias should be considered clinically relevant, we believed that a broad definition for the primary analysis was prudent to avoid missing cases. It is likely that the 12% CTIA incidence reported in our primary analysis represents the high end of the estimate of CTIA. In the secondary analysis, we attempted to exclude the nonspecific arrhythmia diagnoses, and the incidence of CTIA on the basis of the more specific definition was cut by about half, although it was still significantly more common in the anthracycline group than with targeted agents.

Conclusions

In a large cohort of patients being treated with TCAs and anthracyclines, ≈12% developed a new arrhythmia diagnosis within the first 6 months of treatment. Male sex, hypertension, and a history of CHF were all associated with a significantly increased risk of CTIA. In contrast, treatment with a novel, targeted agent was associated with an ≈40% lower risk of developing CTIA compared with anthracyclines.

Disclosures

None.

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