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Chemotherapy induced arrhythmias

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Abstract

Cardio-oncology is a sub-speciality within cardiology that has developed primarily as a consequence of the cardiovascular implications of cancer and its therapeutics. Arrhythmias

are increasingly recognised as an adverse feature of many chemotherapeutic agents. This relationship is poorly defined and studied in the literature as compared to other side effects of chemotherapy. In this review we appraise the published literature on arrhythmogenic consequences of chemotherapeutic agents and summarise the available evidence.

Atrial fibrillation (AF) and other supraventricular tachycardias are frequently observed in patients receiving chemotherapy. High rates of AF are seen with certain agents such as tyrosine kinase inhibitors eg. ibrutinib and the mechanism for this is poorly defined but likely related to off-target effects. The management of AF in cardio-oncology is like that of the non-cancer patient with certain nuances. Mainly that bleeding and stroke risk stratification tools are not validated in the cancer population. In this patient cohort, treatment decisions are usually led by anecdotal evidence rather than an evidence base. This leads to treatment heterogeneity between clinicians. Furthermore, various drug interactions can limit the choice of therapy, particularly with respect to anticoagulant drugs. Many chemotherapeutic agents have been implicated in QT interval prolongation, of these, arsenic trioxide and several tyrosine kinase inhibitors are classic culprits. In patients receiving these agents, it is advisable to perform a baseline ECG and monitor the QT interval. If the QTc increases by 60ms from baseline or is greater than 500ms it is advisable to suspend treatment temporarily. Moving forward, further trials are required in the field of cardio-oncology to better understand the relationship between chemotherapeutic agents and arrhythmia.

Keywords: Atrial fibrillation, Long QTc, Arrhythmia, Cardio-oncology, AF

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1.0 Introduction

Cardiovascular disease (CVD) and oncological disease are two of the leading causes of death worldwide [1, 2]. Over the past half century there have been significant improvements in the survival rates of many cancers. This dramatic increase in survival has been accompanied by an equally dramatic increase in CVD burden in this population. This is likely multifactorial due to 1) increasing survivorship age and 2) downstream side effects of treatment. Cancer treatments in general share several detrimental effects that lead to upregulation of cardiovascular risk factors [3].

Cardiotoxicity secondary to chemotherapeutic agents was first described in the 1960s, where it was noted that patients treated with anthracyclines had a propensity to develop left ventricular systolic dysfunction and pericarditis/myocarditis [4, 5]. Since then, a multitude of cancer therapies have been associated with a variety of cardiovascular side effects [6]. Cardio-oncology is a relatively new field in cardiology born out of this collision with oncology. Cardio-oncologists focus on the diagnosis, prevention, and treatment of the cardiovascular complications of cancer and its treatment. A significant part of their work involves optimising patients with pre-existing CVD prior to their oncological treatment. Cardio-oncologists work alongside oncologists to help facilitate the optimal treatment for patients. CVD is the leading cause of morbidity and mortality in this population second only to recurrent malignancy [7]. In 2009, in increasing recognition of the importance of cardiovascular disease in oncology, the International Cardi-Oncology Society was born [8]. In 2016 the European Society of Cardiology (ESC) published a position paper categorising cardio-oncological disease into nine main categories with arrhythmias representing one of these [9].

Chemotherapy-induced arrhythmia is an under-researched and underrecognised stigmata of chemotherapeutic agents. There are several reasons for this, 1) It is rare that arrhythmias are studied in a controlled fashion pre and post chemotherapy and 2) it is even more rare that cancer therapy studies record patients baseline status and any underlying arrhythmias. Therefore, the evidence base is formulated largely from retrospective analysis and case control studies. Confounding matters is that cancer itself creates an arrhythmogenic focus, with some studies demonstrating much higher rates of AF in cancer patients compared to the general population [10]. The combination of this has resulted in a topic that receives less attention than it warrants, with subsequent under-recognition and under-treatment by clinicians. The focus of this article is to provide a narrative review of the literature with regards to chemotherapy-induced cardiac arrhythmias and their treatments. We have not included arrhythmias confined to isolated case reports and rare/limited observations as it is impossible to establish cause and effect or provide the readership with meaningful evidence-based management.

2.0 Commonly implicated agents

2.1 Alkylating agents

Alkylating agents mechanistically add an alkyl group to the guanine base of the deoxyribonucleic acid molecule causing subsequent damage and stopping proliferation [11]. Alkylating-like agents act similarly; however, they lack the alkyl group. These agents were initially utilised as mustard gas in the second world war. However, subsequently their chemotherapeutic potential was recognised resulting in their utility as the first modern cancer chemotherapy. Examples include cyclophosphamide, chlorambucil, busulfan and cisplatin. A

variety of different cancers are treated with alkylating agents including but not limited to lung, breast, and ovary as well as multiple haematological malignancies.

Cyclophosphamide is well documented to cause acute cardiac toxicity with potentially fatal consequences [12]. Arrhythmia often occurs in the context of perimyocarditis and includes but is not limited to premature ventricular complexes (PVC) and ventricular tachycardia (VT) [13, 14]. Conduction defects can also occur due to damage in the Purkinje system caused by microangiopathy or transient coronary vasospasm[15]. Cisplatin therapy has been associated occasionally with atrial fibrillation (AF) and supraventricular tachycardias (SVT) when given intravenously [16, 17], possibly secondary to its propensity to cause hypomagnesemia. These rates are substantially higher with intrapericardial or intrapleural administration where rates of up to 32% have been reported [18-20]. Melphalan has been implicated in causing AF in around 6.6-22.5% of all patients who undergo treatment [21, 22]. This occurred in patients with structurally normal hearts on echocardiography and negative stress tests [23]. Ifosfamide has been associated with malignant ventricular arrhythmias, possibly secondary to development of congestive cardiac failure [24].

2.2 Anthracyclines

Anthracyclines such as doxorubicin and daunorubicin work by interfering with DNA metabolism. These agents are often used to treat haematological malignancies, ovarian and breast cancers [25]. Anthracyclines are considered one of the main culprits of chemotherapy-induced cardiotoxicity [26, 27]. They can cause a well-recognised dose-dependent left ventricular dysfunction that for many decades was thought to be irreversible [3]. However, this concept has been challenged in recent years and current data would suggest an element of reversibility [28]. Furthermore, the risk of left ventricular dysfunction increases substantially

when other cardiotoxic agents such as trastuzumab are utilised [29]. In one prospective study, 65.5% of patients studied with Holter monitors demonstrated varying arrhythmias following anthracycline use [30]. AF appears to be common, with around 10% of patients suffering an episode in the first course [30]. Other frequently observed arrhythmias included but were not limited to ventricular extrasystoles, atrial extrasystoles and sinus tachycardia [30]. Rarely, VT/ventricular fibrillation (VF) has been reported [31]. Arrhythmias generally occur during and shortly after drug administration and are usually reversible [30, 32]. Most arrhythmias are thought to be secondary to cardiomyopathy rather than primary to anthracycline utilisation [33].

Anthracycline induced arrhythmias have several plausible explanations. The principal theory is increasing oxidative stress, as evidenced by increasing levels of reaction oxygen species and lipid peroxidation. Simultaneously, there is a reduction in in the levels of antioxidants [34]. Furthermore, there are direct electrophysiological effects in action, including a direct action on the Purkinje fibres to decrease the amplitude and prolong the duration of the action potential. This is believed to be secondary to inhibition of the sodium-calcium exchange [35].

2.3 Antimetabolite therapy

Antimetabolite therapy interferes with deoxyribonucleic acid production and inhibits cell division. Common examples include methotrexate, 5-flurouracil (5-FU), fludarabine and capecitabine. These agents are commonly used in the treatment of colorectal, oesophageal, pancreatic and stomach cancers [36]. 5-FU has been implicated in coronary vasospasm with subsequent ischemic electrocardiogram (ECG) changes. This occurs via a direct toxic effect on the vascular endothelium through endothelial nitric oxide synthase, leading to coronary

spasm and endothelium-independent vasoconstriction via protein kinase C. Furthermore, there is evidence that administration of 5-FU leads to increased levels of endothelin-1 which may lead to vasoconstriction and subsequent cardiotoxicity.

[37]. This risk of cardiac ischemia appears to be dose-related with high dose infusions conferring a higher risk profile [38]. Other common ECG manifestations of 5-FU include a prolonged P-wave duration, ST-T wave changes, a decrease in the QRS complex voltage and QTc prolongation [39, 40]. 5-FU has also been implicated in sinus bradycardia/tachycardia, AF, PVCs, VT, and sudden cardiac death (SCD) [40-42]. The majority of these arrhythmias appears to be ischemia driven rather than secondary to chemotherapeutic complications [43]. Capecitabine (a pro-drug of 5-FU) understandably has similar rates of similar arrhythmias as 5-FU and likely a similar mechanism [44]. Gemcitabine has been associated with sinus node and atrioventricular node disease and rarely with VT and subsequent cardiac arrest [45]. A 2020 systematic review demonstrated that episodes of SVT, AF and atrial flutter were commonly seen with AF constituting over 60% of arrhythmogenic events [46]. Cytarabine has in case reports been associated with bradycardia requiring atropine to terminate [47].

2.4 – Tyrosine kinase inhibitors (TKIs)

Tyrosine kinase inhibitors (TKIs), as the name implies work to inhibit tyrosine kinase activity. It is well recognised that deregulated protein tyrosine kinase activity is central to the pathogenesis of human cancers. There are largely 2 classes of TKIs 1) monoclonal antibodies that target growth factor receptor tyrosine kinases 2) direct agents that target both receptor and nonreceptor tyrosine kinases [48]. The most well-known example of a TKIs is imatinib which was one of the first cancer therapies to show the potential of targeted action [49]. However other common examples include ibrutinib, dasatinib, sunitinib and lapatinib. These

agents are frequently utilised in a variety of haematological malignancies including chromic myeloid leukaemia, B-cell lymphoma, and solid cancers such as breast, colorectal and pancreatic cancer [48]. Mechanistically, several TKIs have been observed to block the HERG potassium channels prolonging the ventricular action potential and the QT interval [50].

TKIs have been implicated in a variety of cardiac dysfunction including, but not limited to left ventricular systolic dysfunction with subsequent heart failure, hypertension, and QT prolongation [51]. Furthermore several have been linked to atrial fibrillation and a smaller number linked to bradyarrhythmias and ventricular arrhythmias [52].

QT interval prolongation appears to be a class effect as the majority of TKIs are implicated in varying degrees [53, 54]. This QT prolongation appears to be dose dependent and occurs frequently at the start of therapy and is one of the most common reasons cited for discontinuation [51, 54]. Overall, the risk of significant QTc prolongation is rare, except with a few TKIs that stand out (table 1).

Ibrutinib is a Bruton's kinase inhibitor (BTK) that is a classically associated with AF in up to 16% of patients [55]. Ibrutinib is the mainstay of chronic lymphocytic leukaemia treatment. In a 2021 analysis of 3,663,300 case reports of TKIs, ibrutinib was found to have the strongest association with AF increasing the overall risk by 9-fold [56]. AF is believed to be due to off-target effect on C-terminal Src kinase. In the murine model, ibrutinib has been demonstrated to result in atrial fibrosis, atrial remodelling, and an increase in the atrial refractory period [57]. It is believed that second generation BTK inhibitors, such as acalabrutinib are more specific and avoid C-terminal Src kinase and therefore demonstrate lower rates of AF [57]. Atrial fibrillation can often be a therapy limiting side effect and can

result in significant morbidity [58]. Furthermore, its management is more challenging due to the complex drug-drug interaction between ibrutinib and anticoagulants and antiarrhythmic medications. Therefore in patients suffering AF secondary to ibrutinib it is advised to seek cardio-oncology advice for evidence based management [59]. Rarely, ibrutinib has been associated with VT's and SCD [60].

2.5 Mitotic inhibitors

Mitotic inhibitors act by stabilizing microtubules, thus blocking cell division. Common agents include vinca alkaloids (vincristine and vinblastine) and taxanes (paclitaxel and docetaxel). These agents are utilised in the treatment of various leukaemias, Hodgkin's lymphoma, neuroblastoma, and small cell lung carcinoma [61]. Paclitaxel has been commonly associated with transient sinus bradycardia in around 29% of patients [62]. This is generally unrecognised. It has also been associated with right and left bundle branch blocks with occasional transient complete heart block [63]. Infrequent QTc prolongation has also been reported [64]. Very rarely there have been reports of SVTs and VT [63]. Overall event rates with mitotic inhibitors reported in the literature are low and therefore routine monitoring is not advised [63, 65]. The mechanism of these events is unknown and little researched, but it may be secondary to coronary artery spasm and an increase in cardiac sensitivity to hypoxia [66].

2.6 Proteasome inhibitors

Proteasome inhibition may prevent degradation of pro-apoptotic factors such as the p53 protein, permitting activation of programmed cell death in neoplastic cells dependent upon suppression of pro-apoptotic pathways. Examples include bortezomib and carfilzomib.

These agents are often utilised in multiple myeloma and mantle cell lymphoma. Proteasome inhibitors are well known to cause heart failure and this may be the largest player in causing arrhythmia [67]. Furthermore, proteosome inhibitors lead to atherosclerotic plaque instability due to apoptosis of smooth muscle cells and this may play a role[68]. However overall event rates are small and largely contained to case reports and case series.

2.7 Histone deacetylase inhibitors

The Histone deacetylase inhibitors inhibit the proliferation of tumour cells by inducing cell cycle arrest and apoptosis [69]. Examples include romidepsin and panobinostat. These agents have found utility in the treatment of some T-cell lymphoma and multiple myeloma. A variety of ECG changes have been described with subsequent arrhythmias in the form of SVT, AF, and VT and rarely SCD [70-72]. These events are often short lived and subside prior to the subsequent cycle [71]. The mechanism of action at play for these events is thought to be secondary to an inhibitory effect on HERG channels[72]. In a large study of more than 500 patients, there were 6 cases of SCD, with significant QTc prolongation in 3.5-10% of patients depending on which agent was utilised [73]. In particular, panobinostat has the highest rate of QTc prolongation within this class of drugs [74].

2.8 Miscellaneous chemotherapeutic agents

2.8.1 Amsacrine

Amsacrine's mechanism of action is incompletely defined and related to intercalation into DNA and inhibition of topoisomerase II with secondary cell death. It has been associated with a variety of cardiac abnormalities including QT prolongation, atrial and ventricular arrhythmias, and SCD [75, 76]. The mechanism of this is thought to be inhibition of HERG potassium channels[77]. Events often occur rapidly after the first dose and terminate within

24 hours after drug discontinuation. Overall event rates are low with one study of 5240 patients demonstrating 85 arrhythmia related events [78].

2.8.2 Arsenic trioxide

Arsenic trioxide is utilised in the treatment of relapsing promyelocytic leukaemia. Its mechanism of action is unclear [79]. Within chemotherapeutic agents, arsenic trioxide is the most classically implicated agent. Over 90% have some sort of QT prolongation and in one third of patients this is by greater than 60ms [80]. QT prolongation usually occurs in the first few weeks after infusion and returns to normal by the end of 8 weeks post treatment [80]. Arsenic trioxide has also been implicated in a variety of other ECG changes including QRS widening, non-specific ST-T changes and with sinus bradycardia [81]. The exact mechanism leading to QTc prolongation is unclear, however it is thought to be due to interaction with the normal function of the HERG channel[82]. It is advisable in routine practice to undertake a baseline ECG and electrolytes and monitor the ECG during treatment.

2.8.3 Interferons

Interferons are a group of signalling proteins important in the body's response to infection. In oncology they are often utilised to treat haematological malignancies including but not limited to chronic myeloid leukaemia, hairy cell leukaemia and cutaneous T-cell lymphoma [83]. These agents have rarely been linked to a variety of arrhythmias including AF, PVCs and VT's. The mechanism at thought to be inflammatory and related to a decrease in ATP levels[84]. Arrhythmias were usually reversible after the cessation of treatment and occurred early in the course of treatment [84].

2.84 Interleukin-2 (IL-2)

Interleukin-2 (IL-2) is a cytokine-signalling molecule that is an important part of the body's natural response to infection. It is often utilised in the treatment of malignant melanoma and renal cell carcinoma. IL-2 has been implicated in causing SVT's in approximately 8-15% of patients. This is thought to be secondary to direct myocardial toxicity [85, 86]. AF has frequently been observed in up to 8% of patients and very rarely VT has occurred [85, 87]. It is believed that IL-2 results in an increase in vascular permeability with a fluid shift that results in intravascular volume depletion and subsequent tachycardia to increase cardiac output. This capillary leak syndrome is proposed to be the underlying cause of cardiotoxicity [86, 88].

2.85 Rituximab

Rituximab is an anti-CD20 monoclonal antibody. It has been implicated in bradycardia, AF, SVTs and PVCs [89, 90]. These are often noted during or immediately after the infusion. VT is rarer but has been noted in case reports [91, 92]. Furthermore, cases of complete heart block have also been reported [93].

2.86 Thalidomide

Thalidomide is infamous as an over-the-counter drug that was sold in Europe between 1957-1962 which was subsequently linked to exceedingly high rates of birth defects and withdrawn from the market [94]. Whilst its mechanism of action is unclear, it is an effective agent in the treatment of multiple myeloma, acute myeloid leukaemia and Kaposi's sarcoma [95]. Thalidomide has been implicated in causing bradycardia in around 50% of patients [96]. This appears to be dose dependent and frequently occurs at the start of treatment. The mechanism of action is unclear but may be related to TNF-α inhibition (of the dorsal motor neurons of

the vagus nerve [97]) and subsequent dysregulation of the parasympathetic nervous system [98]. Treatment involves reducing the dose or halting treatment, however rarely a pacemaker has been required [98]. Furthermore, thalidomide has been implicated in causing AF in around 4.7% of patients, and rarely with VT and SCD [99].

3.0 Investigation and diagnosis

Arrhythmias can present in a variety of ways ranging from no subjective symptoms to palpitations to cardiac arrest. In patients undergoing chemotherapy, arrhythmias present more commonly than in the general population and therefore clinicians should have a low threshold to initiate a clinical workup. Further complicating matters is that one of the most common presenting complaints [100], that of palpitations, does not always indicate a cardiac aetiology and can often be secondary to systemic illness, anxiety or psychosomatic disease. Diagnosis can be challenging for a variety of reasons, of which the transient nature of arrhythmias is a large contributing factor. Work-up can often leave patients without a diagnosis and no specific treatment [101]. This can result in a large proportion of patients suffering relapses with subsequent morbidity and mortality. Work-up should incorporate a combination of history, examination and subsequent investigation as felt required by the treating clinician. In one study of 190 patients, around 84% could have an aetiology of their palpitations determined, with around 43% being cardiac in origin. However in those with underlying cardiac disease, this figure rose to 91% [102]. This highlights the importantance in identification of high-risk patients and building an appropriate risk profile.

3.1 History and examination

The history remains the mainstream of the initial assessment and helps categorise patients into high and low risk categories. A thorough history should inquire about factors known to increase the likelihood of arrhythmias such as prior cardiac disease, the relationship between the symptoms and sleep/work and the duration of the symptoms [103]. It is important to look for red flag symptoms such as syncope, exercise-induced palpitations, and a family history of SCD. The role of the examination is limited as arrhythmias are usually transient in nature and absent during a consultation.

3.2 Clinical investigations

All patients undergoing chemotherapy complaining of palpitations should have the following performed

- Routine blood tests including electrolytes and thyroid function tests
- Consideration of an echocardiogram if indicated based on the history
- A baseline 12 lead ECG with subsequent monitoring dependent on the initial risk assessment

We would advise further ambulatory monitoring depending on the patient's symptom load and pre-test probability of cardiac arrhythmia. For example, in patients at much higher risk of cardiac arrhythmia i.e patients on ibrutinib with dilated atria on echocardiography, it would be advisable to undertake prolonged ambulatory monitoring looking for AF. In rare situations, in patients with a very high pre-test probability of a serious cardiac arrhythmia, electrophysiology studies can be performed [104].

4.0 Atrial fibrillation

Atrial fibrillation is the most common cardiac arrhythmia in the general population and in the treated and untreated cancer patient [9, 105]. AF is known to occur twice as often in the cancer patient as compared to healthy controls [106]. Both AF and cancer share many common risk factors including but not limited to advanced age and chronic inflammation. Many chemotherapeutic agents have secondary off-target arrhythmogenic effects implicated in causing AF (Table 2). The management of AF is like that in the non-cancer patient, with some slight caveats. Ultimately, treatment focuses on ameliorating stroke risk and ensuring patients' symptoms are under control. It should be noted that the standard risk assessment tools such as CHA_2DS_2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 [doubled], diabetes, stroke [doubled]–vascular disease, age 65 to 74, sex [female]) and HAS-BLED (hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each)) have not been validated in the cancer population. Therefore, the decision on anticoagulation should not be based purely on these risk assessment scores [9]. This is because the risk of bleeding and thrombosis both fail to be captured by the standard risk assessment scores as cancer and its treatments provide additional difficulty in measuring risk factors. For example, some cancers and some treatments predispose to both bleeding and thrombosis [107]. In complex situations cardio-oncology advice should be sought early.

The AF Better Care (ABC) pathway (Figure 1) can be utilised by clinicians to help guide treatment. A, avoid stroke, B, better symptom control and C, cardiovascular risk factors and co-morbidity [108]. In the cancer population the usual strategy involves rate control unless there are strong reasons for pursuing a rhythm control. The decision on anticoagulation should be made by the patient following an informed discussion with a clinician.

Anticoagulation options include low molecular weight heparins, vitamin K antagonists and direct oral anticoagulants [107].

4.1 – AF secondary to ibrutinib

Ibrutinib is generally well tolerated with a good safety profile, however it dramatically increases the rates of AF whilst simultaneously increasing the risk of bleeding due its effect on von Willebrand factor and therefore warrants its own discussion [109]. In patients receiving ibrutinib we advise they undergo a baseline ECG and echocardiogram and if they develop symptoms it would be prudent to undertake prolonged ambulatory monitoring looking for AF [59]. Generally, AF and ventricular arrhythmias occur within 2-3 months of treatment and therefore monitoring should be more frequent during this period.

Once AF is manifest, management is more complex as ibrutinib can interact with many drugs metabolised by P-glycoprotein or CYP450 3A4. Therefore, cardio-oncology advice is warranted for the optimal management. It is advisable to pursue a rate control strategy and to utilise a direct oral anticoagulant. The medication of choice is either apixaban or edoxoban [59]. In patients at very high risk where anticoagulation is contraindicated, left atrial appendage occlusion may be considered [60].

5.0 QTc prolongation

The QT interval represents the time taken for ventricular depolarisation and repolarisation. Clinically a prolonging of the QT interval can result in Torsades de Pointes (TdP) with

subsequent ventricular fibrillation and sudden cardiac death. This is relevant as many chemotherapeutic agents have been linked to QT prolongation. A full list of QT-prolonging drugs can be found at www.crediblemeds.org. A QTc <450ms in women and a QTc<430ms in men is considered normal in a stable rate. QTc values from 450-470ms in women and from 430-450 in men are considered borderline [110]. Whilst there is no threshold where TdP is certain to occur, each 10ms increase has been linked to an approximately 5-7% increased risk of TdP [111]. Given the exponential risk, values above 500ms are considered dangerous as most recorded events have occurred above this [112].

There are a variety of factors that predispose to QT prolongation including but not limited to older age, female sex, left ventricular hypertrophy and reduced left ventricular ejection fraction, certain medications, ischemia, bradycardia, genetic predisposition, and electrolyte abnormalities such as hypokalaemia, hypomagnesemia, and hypocalcaemia [113-116]. Relevant to the physician is that some of these factors such as electrolyte abnormalities are readily correctable, and others such as sex and age are fixed patient factors. In cancer patients it is imperative that the QT interval and its correctable risk should be controlled before, during and after cancer treatment. We suggest a baseline ECG in all patients undergoing chemotherapy that have a propensity to increase the QTc with subsequent monitoring dependent on the patient's baseline QTc and the risk associated with the chemotherapeutic agent. There is an accepted consensus to temporarily withhold treatment if the QTc >500ms (or <60ms above baseline) and correct the reversible factors [117]. Treatment can often be restarted at a lower dose with more frequent monitoring [9]. The management of a prolonged QTc focuses on withdrawal of the offending agent and correction of the reversible factors.

6.0 Conclusion

Arrhythmias secondary to chemotherapy are common, poorly recognised, and poorly managed. Arrhythmias can have significant impact on morbidity and mortality due to symptoms induced by heart failure, stroke, or death. Furthermore, traditional treatments may not be possible given the complexity of these patients. Therefore, it is important to undertake simple measures to reduce the arrhythmogenic risk for this population. We advise a routine cardiovascular risk assessment prior to initiation of chemotherapy and a referral to cardio-oncology in the high-risk patient. AF is the commonest arrhythmia in patients undergoing cancer treatment and its management can be challenging due to a lack of evidence on the appropriate strategies. Moving forward chemotherapy trials need to record cardiovascular outcomes and arrhythmia events so that the evidence base becomes clearer.

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Table 1 – Tyrosine kinase inhibitors (TKIs) and their propensity to cause QTc prolongation

Type of TKI	Percent of total number of patients with QTc prolongation	Percent of total number of patients with QTc 60ms greater than baseline	Percent of total number of patients with QTc greater than 500ms	Percent of total number of patients suffering VT/SCD/TdP
Imatinib	1-5%	N/A	0.02%	Described
Lapatinib	1.7%	0.02	N/A	N/A
Nilotinib	5-25%	1-4.7%	1%	N/A
Pazopanib	N/A	N/A	2	<1%
Sunitinib	19.4%	3.8%	3.8%	3.8%
Vandetanib	16.4%	12-15%	4-8%	Described
Vemurafenib	5%	1.6	2.3%	0.006

VT, ventricular tachycardia; SCD, sudden cardiac death; TdP, Torsades de pointes. [62, 112-115]

Table 2 – Symptoms that can be attributed to arrythmias
Fatigue and weakness
Dizziness and light-headedness
Syncope/presyncope
Palpitations
Dyspnoea
Chest pain / chest discomfort
Cardiac arrest
No subjective symptoms

Tyrosine kinase inhibitors – in particular, ibrutinib
Alkylating agents
Anthracyclines
Antimetabolites
Mitotic inhibitors
Monoclonal antibodies
Proteasome inhibitors
Histone deacetylase inhibitors
Interferons
Interleukin-2
Table 3 – chemotherapeutic agents implicated in causing atrial fibrillation