Bradyarrhythmias in Cardio-Oncology

Marta Fonseca[1,2]   Evaline Cheng[3,©]   Duc Do[3]   Shouvik Haldar[4,5]   Shelby Kutty[6]   Eric H. Yang[3]
Arjun K. Ghosh[1,2#]   Avirup Guha[7,8,9#,©]

[1]Division of Cardiology Cardiac-Oncology Service, Bart's Heart Centre, St Bartholomew's Hospital West Smithfield, London, United Kingdom
[2]Hatter Cardiovascular Institute, Institute of Cardiovascular Science UCL, University College London Hospital, London, United Kingdom
[3]UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California, Los Angeles, Los Angeles, California, United States
[4]Division of Cardiology Heart Rhythm Centre, The Royal Brompton and Harefield Hospitals, Guys & St Thomas' NHS Foundation Trust, London, United Kingdom
[5]National Heart and Lung Institute, Imperial College, London, United Kingdom
[6]The Helen B. Taussig Heart Center, The Johns Hopkins Hospital and Johns Hopkins University, Baltimore, Maryland, United States

Address for correspondence Avirup Guha, MD, Harrington Heart and Vascular Institute, Case Western Reserve University, 11100 Euclid Ave, Cleveland, OH 44106, United States (e-mail: avirup.guha@case.edu).

[7]Harrington Heart and Vascular Institute, Case Western Reserve University, Cleveland, Ohio, United States
[8]Division of Cardiology, Department of Medicine, Augusta University, Augusta, Georgia, United States
[9]Division of Cardiology-Oncology Program, The Ohio State University, Columbus, Ohio, United States

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Abstract

Avirup Guha

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The relationship between bradyarrhythmias and cancer therapies has not been well described but is increasingly recognized. There have been extensive advances in oncological pharmacotherapy, with several new classes of drugs available including targeted agents, immune checkpoint inhibitors and CAR T cell therapy. This increasing repertoire of available drugs has revolutionized overall prognosis and survival of cancer patients but the true extent of their cardiovascular toxicity is only beginning to be understood. Previous studies and published reviews have traditionally focused on conventional chemotherapies and in arrhythmias in general, particularly tachyarrhythmias. The number of patients with both cancer and cardiovascular problems is increasing globally and oncologists and cardiologists need to be adept at managing arrythmia based scenarios. Greater collaboration between the two specialties including studies with prospective data collection in Cardio-Oncology are much needed to fill in knowledge gaps in this arena. This case-based review summarizes current available evidence of cancer treatment-related bradyarrhythmia incidence (including its different subtypes), possible mechanisms and outcomes. Furthermore, we propose a stepwise surveillance and management protocol for patients with suspected bradyarrhythmia related to cancer treatment.

Joint senior authors.

Case 1: Bradycardia with Antithymocyte Globulin

A 30-year-old male with aplastic anemia started treatment with antithymocyte globulin (ATG). He had no significant cardiovascular risk factors or cardiovascular disease. On the first ATG cycle, his heart rate dropped to 40 bpm (no electrocardiogram recorded at this point). He remained asymptomatic from the cardiac perspective. The Oncology team referred the patient to the Cardio-Oncology clinic. The echocardiogram and the 24-hour Holter monitoring performed 7 days after the bradycardic episode were normal. Bradycardia is an uncommon cardiotoxic sequelae of ATG, with current data limited to some case reports and one series.[1] We suggested admission with cardiac monitoring during the next ATG cycle.

Bradycardia and Bradyarrhythmias with Conventional Chemotherapies and Targeted Agents

Bradyarrhythmias have been reported in patients treated with alkylating agents. Four out of 39 patients with breast cancer, previously treated with anthracyclines and receiving high-dose chemotherapy with cyclophosphamide before stem cell transplantation, developed some degree of atrioventricular block (AVB).[2] Two of them developed complete heart block (CHB) managed with isoproterenol infusion, but in all cases, the conduction abnormality was transient, and the patients were able to complete the scheduled regimen. Nevertheless, other reports of CHB required discontinuation of cyclophosphamide and/or temporary as well as permanent pacemaker implantation.[3,4] Arrhythmias related to alkylating agents are thought to arise from direct cardiotoxicity to myocytes and ischemic damage caused by coronary vasospasm and vascular endothelial injury with subsequent intracapillary microthrombi. An increased vagal tone has also been proposed as a mechanism given that some patients have uncontrolled emesis associated with CHB.[5,6]

Anthracyclines are traditionally associated with cardiomyopathy/left ventricular dysfunction, with arrhythmias resulting from the former. In a prospective study of patients receiving doxorubicin, 3.4% developed bradycardia detected by 24-hour Holter monitoring with one patient developing CHB requiring permanent pacing.[7] There have been no specific studies addressing the mechanisms of bradyarrhythmias due to anthracyclines. Anthracyclines can have a direct electrophysiological effect by interfering with cardiac Ca^{2+} channels. They also generate, lead to the accumulation of and increase cardiomyocyte's susceptibility to reactive oxygen species. Abnormal Ca^{2+} homeostasis due to abnormal functioning of sarcoplasmic reticulum calcium–ATPase can cause intracellular Ca^{2+} overload and subsequent myocardial necrosis. Reduction in adenosine monophosphate-activated protein kinase expression can lead to myocardial apoptosis. Cardiac accumulation of doxorubicinol, a toxic metabolite of doxorubicin, may be involved in some of these mechanisms.[5,6]

Cisplatin infusion is associated with sinus bradycardia (SB) which can start immediately during infusion, can be marked, and tends to recur with each cycle.[8-11] Coronary vasospasm, endothelial damage, and electrolyte disturbances are postulated mechanisms for cisplatin cardiotoxicity.[5,6] Cisplatin deposition in the sinoatrial (SA) node and the vasculature supplying it are likely to be the cause of the bradycardia.[8]

There have been isolated case reports of SB related to 5-fluorouracil (5-FU) treatment with a published case series of six patients that developed asymptomatic SB with a heart rate below 50 bpm. Two of them required repeated interruptions of the infusion, and two of them required discontinuation of the drug due to sustained bradycardia in the second cycle of drug administration.[12] In a second case series of six patients, one of them developed Mobitz type I and another one SB with first-degree AVB. Interestingly there were no ST-segment changes, and troponin levels were normal.[13] A relatively large retrospective study showed that 5-FU induced SB occurred in 12% of the patients (36 out of 301 patients), and it was the most common cardiotoxicity.[14] In a prospective study including patients treated with either 5-FU or oral capecitabine, 26 out of 644 (4.03%) had cardiotoxicity, and three of them had conduction abnormalities that included either Mobitz type II or CHB, with one death occurring because of high-grade AVB and subsequent cardiac arrest.[15] The classic mechanism of 5-FU mediated cardiotoxicity is coronary vasospasm either through a direct toxic effect involving endothelial nitric oxide synthase or through endothelium-independent protein kinase C vasoconstriction. Another postulated mechanism is ischemia due to arteritis and/or thrombosis.[5,6] There is a paucity of data regarding bradycardia and other drugs of the antimetabolites class with only one case report of symptomatic SB with cytarabine.[16]

The most common paclitaxel-related arrhythmia is SB, which can occur in as much as 29% of the patients (13 out of 45 patients in one prospective study) but is usually transient and asymptomatic.[17] More advanced AVB is infrequent. In the National Cancer Institute database, including more than 4,000 patients, only four had second- or third-degree AVB. Paclitaxel-induced conduction abnormalities might be explained by reduced coronary blood flow due to vasoconstriction. Histamine-induced release can also cause bradycardia and atrioventricular (AV) conduction delays.[5,6]

CHB requiring pacing to continue arsenic trioxide treatment has been described, but it is infrequent, and the most common described cardiotoxicity of this drug still is QT interval changes.[18] Arsenic trioxide increases Ca^{2+} currents, inhibits K^+ channels, and reduces surface expression of the human ether-a-go-go-related K^+ channels, although these actions are more clearly related to the QTc changes previously mentioned.[5,6]

Isolated cases of varying degrees of AVB have been described with interleukin-2, and it has been speculated that lymphoid infiltration of the AV node or the conduction system of the heart might be at its origin.[19]

In a phase II multicenter study, three out of 131 patients with mantle-cell lymphoma developed bradycardia related with rituximab, requiring some form of treatment.[20] Two case reports of CHB have been published, but one of the patients had previous conduction disease, and the other was an aged patient; hence the causality is difficult to ascertain.[21,22]

It was postulated that rituximab might affect the cardiac conduction system by inhibiting Ca^{2+} channel properties of the CD20 antigen on cardiac myocytes.[22]

In an extension of a phase II study, including 63 relapsed multiple myeloma patients treated with bortezomib, one case of nonspecified and CHB was reported.[23] In another study, two out of 69 patients with multiple myeloma treated with bortezomib developed nonspecified CHB, leading to pacemaker implantation.[24] Bortezomib upregulates the adrenergic G-protein-coupled receptor kinase 2 (GRK2), which can predispose to bradyarrhythmia and AV conduction abnormalities.[5,6]

SB is a common cardiotoxicity of thalidomide and occurred in as many as 53% of the patients included in one study. Although it usually resolved with discontinuation of the drug, some patients required pacemaker implantation.[25,26] AVB is limited to rare case reports.[27] It has been hypothesized that thalidomide inhibits dorsal motor neurons of the nucleus of the vagus nerve by reducing TNF-alfa levels, with subsequent parasympathetic over-reactivity. Bradycardia has also been associated with thalidomide-induced hypothyroidism.[5,6]

Tyrosine kinase inhibitors (TKIs) are implicated in the modulation of growth factor signaling and, as such, play an essential role in targeted cancer therapy. However, they are not entirely selective for protein kinases in cancer cells. SB is therefore observed with various TKIs but is particularly common with ALK-TKIs. In a retrospective analysis of two multinational trials, SB occurred in 42% of the patients treated with crizotinib, with an average decrease in heart rate of 25 bpm. The likelihood of experiencing SB was higher among patients with a pretreatment heart rate of less than 70 bpm.[28] Alectinib treatment resulted in a mean decrease of heart rate of 11 to 13 beats per minute. In approximately 5% of the patients, bradycardia or SB's adverse events were reported, but when analyzing electrocardiograms (ECG), 20% of the patients had heart rates below 50 bpm. Bradycardia is usually transient and asymptomatic and does not require discontinuation of the drug.[29] The occurrence of AVB needing further management is low. In a phase II trial of 295 patients who received lorlatinib, 1% experienced AVB, and 0.3% experienced Grade 3 AVB and underwent pacemaker placement.[30] Symptomatic bradyarrhythmias that led to pacemaker implantation occurred in 1% (three out of 449) of the patients treated with ponatinib.[31] Arrhythmias including AVB are described as common with the use of nilotinib, but the specific percentage of each arrhythmia type is not specified.[32]

►Table 1 summarizes the type and incidence of bradycardia/bradyarrhythmia with each class of agents, as well as the mechanism behind it.

Case 2: CHB with Pembrolizumab

A 65-year-old male with a background of hypertension, diabetes, obesity, and smoking history was diagnosed with metastatic gastric adenocarcinoma and was receiving palliative treatment with pembrolizumab. He then presented to the emergency department with a 2-day history of progressive worsening exertional dyspnea leading to shortness of breath at rest, lightheadedness, and dizziness. The patient received two cycles of pembrolizumab beginning 6 weeks prior. On admission, vital signs were stable, and a physical exam was notable for irregular heart rhythm and trace bilateral lower extremity pitting edema. The ECG showed CHB with a heart rate of approximately 50 bpm and multiple premature ventricular contractions (►Fig. 1). Cardiac troponin I, creatinine kinase, liver enzymes, and C-reactive protein were elevated. A bedside echocardiogram revealed mildly impaired systolic function (left ventricular ejection fraction [LVEF] approximately 50% with anteroseptal hypokinesis with an LVEF of 65% from a prior echocardiogram). Given concerns for acute coronary syndrome (ACS) with electrical instability, the catheterization laboratory was activated. After input from both the cardiology and oncology teams, the patient received only 1 mg/kg prednisone before the procedure for empiric ICI myocarditis to avoid the risks of pulse dose steroids if the final diagnosis was, in fact, an ACS. The patient was found to have nonobstructive coronary artery disease. A temporary–permanent pacemaker was placed in conjunction with immediate pulse IV methylprednisolone treatment in the catheterization laboratory. After additional immunosuppressive therapy (mycophenolate mofetil) and intravenous immunoglobulin therapy, the patient's AV conduction returned to normal after 1 week, and the pacemaker was removed.

Bradycardia and Bradyarrhythmias with Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) are part of a relatively novel drug category which has demonstrated efficacy in prolonging overall survival in numerous cancers with previous poor prognosis. Conceptually, cancer cells can evade the patient's immune system. ICIs aim to restore antitumor immune response by blocking immune checkpoints, i.e., intrinsic downregulation of immunity, such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T lymphocyte-associated protein 4 (CTLA-4). By suppressing immune regulation and tolerance, ICIs are traditionally associated with immune-related adverse events (irAEs). There are concerns that cardiovascular events were not consistently reported in randomized control trials of ICIs.[33] Moreover, there are other cardiotoxic effects related to ICIs besides myocarditis that were likely not identified in registration trials, owing to their limited power.[34] Cardiovascular toxicity is infrequent when compared with other irAEs, but now it is increasingly reported in the literature, and with the rapidly expanding indications of ICIs, we should expect to see these more often.

There are no retrospective studies regarding bradyarrhythmias and the use of ICIs. Most of the published data in relation to cardiovascular toxicities have focused on myocarditis, with some of them reporting concomitant conduction disease but not in a systematic fashion, so the type of bradyarrhythmia, risk factors, treatment, and the outcome are not always clear.

Escudier et al published in 2017 a review of 30 cases of ICIs cardiotoxicity from their cardio-oncology clinic combined

Table 1 Bradycardia/bradyarrhythmia type, incidence, and mechanism with conventional chemotherapy and targeted agents[5,686]

Agent	Adverse event		Incidence of adverse event	Mechanism
	Sinus bradycardia	Atrioventricular block		
Alkylating agents				
Cyclophosphamide	+	+	ND	Endothelial damage, myocardial ischemia, direct cardiotoxicity to myocytes, increased vagal tone.
Ifosfamide	+	–	ND	
Busulfan	–	+	ND	
Anthracyclines	+	+	Bradycardia 3.4%	Abnormal Ca^{2+} homeostasis, cardiac apoptosis, mitochondrial injury, oxidative stress.
Cisplatin	+	+	<1%	Coronary artery vasospasm, electrolyte disturbances, autonomic nervous system imbalance.
Antimetabolites				
5-FU	+	+	SB up to 12%, AVB ND	Coronary ischemia (vasospasm, thrombosis due to endothelial damage).
Capecitabine	+	+	SB in 4.03% (5-FU or Capecitabine), AVB ND	
Clofarabine	+	–	ND	
Cytarabine	+	–	ND	
Fludarabine	+	–	ND	
Pentostatin	+	–	ND	
Paclitaxel	+	+	SB up to 29%, AVB 0.11%	Reduced coronary blood flow due to vasoconstriction, histamine-induced release.
Arsenic trioxide	–	+	ND	Hman ether-a-go-go-related gene (hERG) channel blockade, abnormal Ca^{2+} homeostasis.
Interleukin-2	+	+	ND	Lymphoid infiltration of the atrioventricular node or the conduction system.
Monoclonal antibodies				
Rituximab	+	+	<1%	Inhibition of calcium channel properties of the CD20 antigen on cardiac myocytes.
Alemtuzumab	+	–	SB 1–10%	–
Cetuximab	+	–	SB <1%	–
Pertuzumab	+	–	SB <1%	
Trastuzumab	+	–	SB <1%	
Proteasome inhibitors				
Bortezomib	+	+	ND	Upregulation of GRK2
Carfilzomib	+	+	ND	–
Immunomodulatory drugs				
Thalidomide	+	+	SB >10%, AVB ND	Parasympathetic over-reactivity, thalidomide-induced hypothyroidism
Lenalidomide	+	–	ND	–

(Continued)

Table 1 (*Continued*)

Agent	Adverse event		Incidence of adverse event	Mechanism
	Sinus bradycardia	Atrioventricular block		
Multi-target kinase inhibitors (TKIs)				
Alectinib	+	−	SB 5.1–20%	−
Ceritinib	+	−	SB 3%	
Crizotinib	+	−	SB 5–69%	
Brigatinib	+	−	Bradycardia 5.7–8.1%	
Lorlatinib	−	+	ND	
Nilotinib	+	+	Bradycardia 1–10%	−
Ponatinib	+	+	Symptomatic bradycardia 1%	
Bosutinib	+	−	ND	
Pazopanib	+	−	Bradycardia 19%	−
Sorafenib	+	+	<1%	
Sunitinib	+	−	<1%	
Vemurafenib	+	−	<1%	−
Trametinib	+	−	1–19%	−
Ruxolitinib	+		<1%	−
Histone deacetylase inhibitors				
Panobinostat	+	−	ND	−
Romidepsin	+	−	ND	−
Vorinostat	+	−	ND	−
Amsacrine	+	−	ND	−

Abbreviations: AVB, atrioventricular block; FU, fluorouracil; GRK2, G-protein-coupled receptor kinase 2; ND, not defined; SB, sinus bradycardia.
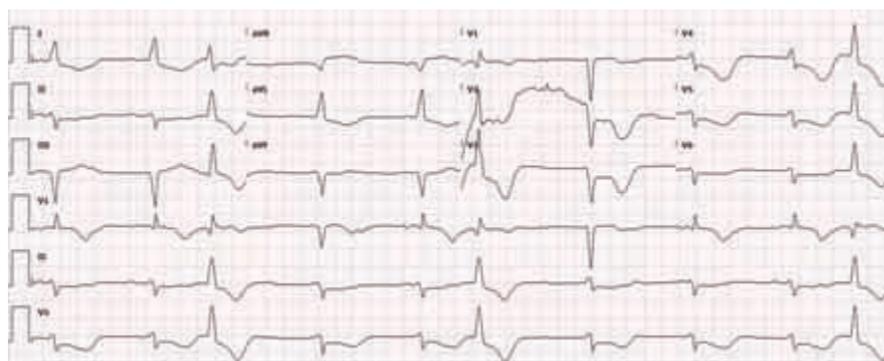

Fig. 1 Immune checkpoint inhibitor-induced bradyarrhythmia ECG (case 2). ECG, electrocardiogram.

with selected cases from a literature review. Of those, 17% (*n* = 5) had conduction abnormalities. Cardiotoxicity was diagnosed 65 (2–454) days after the initiation of ICIs. Cardiovascular mortality was significantly associated with conduction abnormalities (80 vs. 16%; *p* = 0.003).[35]

In a retrospective study conducted using VigiBase, which is the World Health Organization's global database of individual case safety reports, Salem et al. reported an incidence of ICI-related cardiac conductive disorders of 0.12%, similar to the incidence in the entire database.[36]

In a multicenter observational study that included 35 patients with ICI-associated myocarditis, three had hemodynamically significant CHB. Myocarditis was diagnosed at a median of 34 days after initiation of ICIs. Diabetes, sleep apnea, obesity, and combination checkpoint blockade were all identified as risk factors for myocarditis.

In a 2018 systematic review of published case series and case reports, Mir et al concluded that myocarditis was the most commonly observed cardiovascular irAE, corresponding to 45% (n = 45) of the cases. Conduction disease was present in 12% (n = 12) of the patients with cardiovascular toxicities. Of those, three had isolated rhythm disturbances, and nine had another toxicity. The overall mortality rate was 35%, and 50% in patients presenting with CHB or other conduction abnormalities.[34]

In a 2019 review by Atallah-Yunes et al, of 42 myocarditis cases related to pembrolizumab, nivolumab, or ipilimumab use, CHB occurred in 36% of them. In agreement with previously published data, 33% of the myocarditis cases occurred after a single ICI dose and 29% after two doses. Notably, CHB occurred in 64% of the patients that died, and 60% of those who developed CHB died.[37]

A recent study by Zlotoff et al. found that QRS duration is increased in ICI myocarditis and is associated with an increased risk of major adverse cardiac events, including CHB (HR 3.28, 95% CI 1.98–5.62, p < 0.001).[38]

The large majority of bradycardia cases related to ICIs use are due to CHB, with most of the patients having concomitant myocarditis. ►Table 2 describes the characteristics and outcomes of ICIs-related bradycardia case reports and case series. Most strikingly, half of the patients with bradyarrhythmia died; however, it is not clear if this association only denotes the severity of the myocarditis behind it. Definitive pacemakers were inserted in almost two-thirds of the patients, but there are three reported cases of recovery of intrinsic sinus rhythm after steroid therapy.[39-41]

The exact mechanism(s) of ICI-related conduction disease is not fully understood. It is postulated that myocarditis, pre-existing cardiovascular diseases, past cardiotoxic chemotherapy, myocardial metastases, old age, and systemic inflammatory conditions could all contribute to arrhythmias in cancer patients treated with PD-1/PDL-1 inhibitors.[42] Lyon et al hypothesized that ventricular myocarditis, inflammation of the His-Purkinje conduction system, either via direct T-cell-Purkinje interactions or via activation of local macrophages resident in the Purkinje system, increased systemic inflammatory state (without myocarditis), left ventricular impairment due to noninflammatory functional cardiotoxicity, or inflammation of myocardial metastases (if present) could all be at the origin of arrhythmias in the context of ICIs use.[43] In murine models, the deletion of PD-1 leads to autoimmune dilated cardiomyopathy.[44] Later studies detected circulating autoantibodies against cardiac troponin I in PD-1 knockout mice.[45] CTLA-4 knockout mice also develop autoimmune myocarditis with CD4+ and CD8+ T lymphocyte infiltration of the myocardium.[46] In mice models of T cell-mediated myocarditis, there is upregulation of myocardial PD-L1. ICIs can interfere with this likely cytokine-induced cardioprotective mechanism by blocking PD-L1.[47] Johnson et al. described a robust T-cell infiltration, activation, and clonal expansion across the myocardium, striated muscle, and tumor tissue, with shared high-frequency T-cell receptors, in their two reported cases of myocarditis with ICIs use. They then postulated that T cells could either be targeting an antigen shared by those tissue types or that the same T-cell receptor was targeting a tumor antigen and a different but homologous muscle antigen. Backing the first possibility was the fact they observed high levels of muscle-specific antigens (desmin and troponin) in tumors from both patients. However, they still considered the possibility that their finding of clonal, high-frequency, T-cell receptor sequences across tumor and muscle samples could be misleading and that distinct T-cell receptors were targeting dissimilar antigens.[48]

Case 3: Mobitz Type II AVB with Radiation Therapy

A 51-year-old female with a history of stage IIIA nodular sclerosing Hodgkin's lymphoma 32 years ago, stage IIA estrogen-receptor-negative right-sided breast cancer 12 years ago, and radiation-induced mitral stenosis presented after an episode of syncope. Her Hodgkin's lymphoma was previously treated with MOPP (mechlorethamine, oncovin, procarbazine, and prednisone) chemotherapy and mediastinal and mantle field radiation therapy. Her breast cancer was previously treated with AC-T (doxorubicin, cyclophosphamide, and paclitaxel) chemotherapy with subsequent bilateral mastectomy. After this syncopal episode, a 14-day ECG patch was ordered and showed six episodes of Mobitz type II AVB. At that time, the patient was on metoprolol succinate (50 mg daily) for inappropriate sinus tachycardia, which was discontinued. Four months later, the patient was admitted after a recurrent episode of syncope. ECG showed sinus tachycardia at a ventricular rate of 117 bpm with Mobitz type II, underlying right-bundle branch block, and right atrial enlargement (►Fig. 2). Inpatient continuous telemetry revealed additional periods of 2:1 AVB with suspected infra-Hisian disease. She subsequently underwent successful implantation of a dual-chamber pacemaker with a left bundle branch pacing lead. The patient has not had any recurrent syncopal episodes since pacemaker implantation at the time of publication.

Case 4: Mobitz 2:1 AVB with Radiation Therapy

A 54-year-old female with a history of Hodgkin's lymphoma 27 years ago, radiation-induced aortic stenosis, type 2 diabetes mellitus, hyperlipidemia, and hypothyroidism presented with progressive dyspnea on exertion. Her Hodgkin's lymphoma was previously treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy and mediastinal and neck radiation therapy. Subsequently, the patient developed radiation-induced moderate to severe aortic stenosis and aortic insufficiency with associated symptomatic heart failure with preserved ejection fraction. After persistent dyspnea refractory to medical management, the patient was admitted to evaluate the suitability of transcatheter aortic valve replacement (TAVR). During this admission, ECG showed normal sinus rhythm with 2:1 AVB and right-bundle branch block with a ventricular rate of 45 bpm, concerning for infra-Hisian disease (►Fig. 3). Inpatient continuous telemetry showed persistency of the rhythm

Table 2 Case reports and case series of bradycardia and bradyarrhythmia related to immune checkpoint inhibitors

	Age	Sex	Cancer	ICI	Number of cycles	Bradyarrhythmia	Pacemaker	Cardiovascular risk factors/cardiovascular disease/past medical history	Laboratory markers	Imaging studies	Histopathology	Treatment	Death
Tshuma et al[87]	74	Female	Urothelial (bladder) cancer	Atezolizumab	12	Varying degree of AV block	Yes	Sleep apnea, hypopituitarism	–	Mild LV impairment on CMR	–	Steroids	Yes
Bukamur et al[88]	88	Female	Squamous cell lung carcinoma	Nivolumab	2	Complete AV block	Yes	Hypertension, hyperlipidemia	High CK and troponin	Increased wall thickness on TTE	–	Steroids	No
Prevel et al[89]	80	Male	Squamous cell lung carcinoma	Nivolumab	4	Complete AV block	No	Smoker, hypertension, diabetes mellitus type 2	High CK	–	–	No	Yes
Tan et al[90]	74	Male	Nonsmall cell lung cancer	Nivolumab	2	Complete AV block	Yes	Smoker, chronic obstructive pulmonary disease	High troponin and BNP	LVEF 31% on TTE, increased T2 on CMR	–	Steroids	No
Behling et al[91]	63	Male	Melanoma	Nivolumab	2	Complete AV block	Yes	Chronic obstructive pulmonary disease, hypertension, hyperlipidemia, diabetes mellitus type 2	High CK and troponin	Increased wall thickness on TTE	–	Steroids	No
Samara et al[92]	77	Male	Melanoma	Ipilimumab	4	Junctional bradycardia	No	Hypertension	High troponin and BNP	LVEF 45% on TTE	–	Steroids	Yes
Johnson et al[48]	65	Female	Melanoma	Nivolumab + ipilimumab	1	Complete AV block	No	Hypertension	High CK and troponin	LVEF 73% on TTE	Patchy lymphocytic infiltrate within the myocardium, cardiac sinus, and atrioventricular nodes.	Steroids	Yes

(Continued)

Table 2 (Continued)

	Age	Sex	Cancer	ICI	Number of cycles	Bradyarrhythmia	Pacemaker	Cardiovascular risk factors/ cardiovascular disease/past medical history	Laboratory markers	Imaging studies	Histopathology	Treatment	Death
Johnson et al[48]	63	Male	Melanoma	Nivolumab + Ipilimumab	1	Complete AV block	Yes	Hypertension	High troponin	LVEF 73% on TTE	Patchy lymphocytic infiltrate within the myocardium, cardiac sinus, and atrioventricular nodes.	Steroids and Infliximab	Yes
Hardy et al[93]	81	Male	Renal cell carcinoma	Nivolumab + Ipilimumab	1	Complete AV block	Yes	–	High CK and troponin	LVEF 60–65% on TTE	CD3-positive T cells, occasional CD20-positive B cells, and CD68-positive macrophages. More CD4-positive cells as compared with CD8-positive cells. Staining with antibodies to PD-1 and PD-L1 in the areas of inflammation.	Steroids and plasmapheresis	Yes
Yanase et al[41]	59	Male	Renal cell carcinoma	Nivolumab + ipilimumab	1	Transient complete AV block	No	–	High CK and troponin		–	Steroids, plasmapheresis, and IV immunoglobulin (concomitant MG)	No
Szuchan et al[94]	70	Female	Thymic carcinoma	Pembrolizumab	1	Complete AV block	Yes	–	High CK and troponin	LVEF 63% on TTE	Lymphocyte infiltration of the myocardium	Steroids and plasmapheresis (concomitant MG)	No

(Continued)

Table 2 (*Continued*)

	Age	Sex	Cancer	ICI	Number of cycles	Bradyarrhythmia	Pacemaker	Cardiovascular risk factors/cardiovascular disease/past medical history	Laboratory markers	Imaging studies	Histopathology	Treatment	Death
Katsume et al[40]	73	Male	Nonsmall cell lung cancer	Pembrolizumab	1	Complete AV block	No	–	High CK and troponin	LVEF 70%	–	Steroids	No
Lee et al[95]	37	Female	Alveolar soft part sarcoma	Pembrolizumab	13	Sinus bradycardia	No	–	Normal troponin	LVEF 60–65% on TTE; High T2 on CMR	–	Steroids	No
Agrawal et al[96]	73	Male	Mesothelioma	Pembrolizumab	1	Complete AV block	Yes	–	High CK and troponin	LVEF 50–60%	–	Steroids, plasmapheresis and IV immunoglobulin (concomitant MG)	Yes
Agrawal et al[96]	89	Male	Melanoma	Pembrolizumab	1	Complete AV block	Yes	Hypertension, hyperlipidemia, diabetes mellitus type 2	High CK, troponin, and BNP	Normal TTE	–	Steroids and IV immunoglobulin	Yes
Khan et al[78]	67	Female	Nonsmall cell lung cancer	Pembrolizumab	1	Complete AV block	Yes	Hypertension and hyperlipidemia	Normal CK, troponin, and BNP	LVEF 60–65% on TTE	–		No
Mahmood et al[39]	75	Female	Endometrial cancer	Durvalumab + tremelimumab	1	Transient complete AV block	No		High CK and troponin	LVEF 54%	–	Steroids and MMF	No

Abbreviations: AV, atrioventricular; CK, creatine kinase; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction; MG, myasthenia gravis; MMF, mycophenolate mofetil; TTE, transthoracic echocardiography.
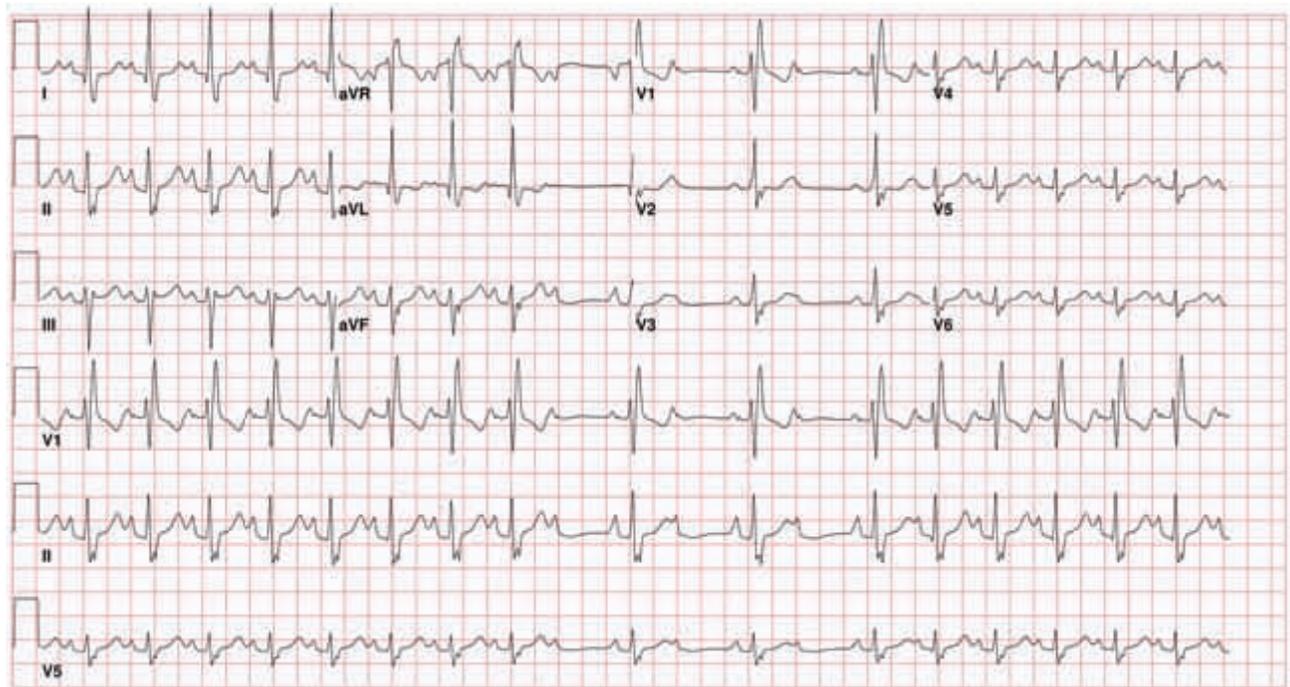
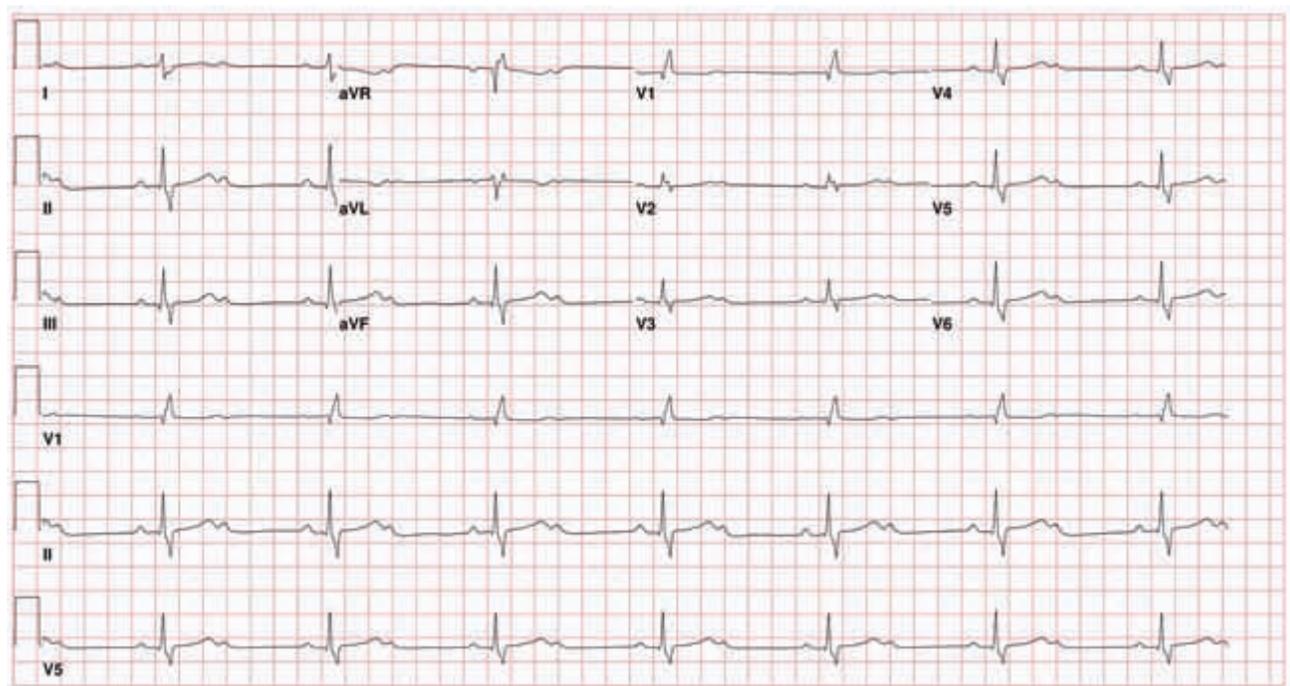**Fig. 2** Radiation-induced bradyarrhythmia ECG (case 3). ECG, electrocardiogram.

Fig. 3 Radiation-induced bradyarrhythmia ECG (case 4). ECG, electrocardiogram.

disturbance. She subsequently underwent successful implantation of a dual-chamber pacemaker with left bundle branch pacing lead before TAVR.

Bradycardia and Bradyarrhythmias with Radiation Therapy

Radiation therapy for thoracic malignancies such as Hodgkin's lymphoma, left-sided breast cancer, lung cancer, and other mediastinal tumors can lead to radiation-associated cardiac disease due to unwanted cardiac exposure.[49] SB and bradyarrhythmia can develop from the direct effects of irradiation on the conduction system and myocardium, often manifesting years to decades after the radiation treatment.[50] In 48 patients with Hodgkin's lymphoma treated with mediastinal irradiation, 75% had conduction defects on ECG with a mean follow-up of 14 years.[51] Case series for other patients with irradiation for Hodgkin's lymphoma 10 to 20 years prior described the development of CHB, predominantly due

to infranodal conduction block.[52-54] Other types of bradyarrhythmia after mediastinal irradiation include first-degree and Mobitz type II AVB.[54] Right bundle branch block was also commonly observed due to its anterior location.[52,55] Second- and third-degree AVB have also been reported after irradiation for left-sided breast cancer 18 to 23 years prior.[56] Valvular disease is also a latent consequence of radiation therapy. Radiation-associated valvular thickening and calcification can lead to stenosis or regurgitation, more commonly affecting left-sided valves. The mechanism for radiation-associated bradyarrhythmia is primarily driven by damage to the conduction system from chronic, progressive fibrosis.[49] Reactive oxygen species are formed from radiation exposure, creating an inflammatory response.[57] Subsequently, progressive fibrosis and endothelial dysfunction are enhanced by the induction of transforming growth factor-β expression.[58] Experiments of irradiation in animal models have shown increased deposition of collagen in the myocardium, which exacerbates over time.[59] Similar findings are observed in patients with CHB who underwent autopsy. Microscopic examination of the conduction system of patients with CHB after mediastinal irradiation showed sclerosis of the SA node arterioles and arteries, moderate fibrosis near the SA and AV nodes, and substantial fibrosis of both right and left bundle branches.[53,54]

Interaction between Anticancer Agents and Nodal Blocking Drugs

A drug–drug interaction occurs when the combined administration of drugs leads to an adverse pharmacological or clinical response in patients.[60] Patients with cancer have an increased risk of potential drug–drug interactions due to polypharmacy among anticancer therapies and medications for comorbidities as well as age-related physiologic changes that alter drug absorption or excretion.[60,61] In particular,

drug–drug interactions have been reported in 14 to 16% of patients receiving anticancer therapy.[62,63] Pharmacodynamic interactions occur when two or more drugs have similar physiological outcomes, leading to excessive response or toxicity. Pharmacokinetic interactions occur when one drug alters the absorption, distribution, metabolism, or elimination of another drug. Commonly, metabolism by cytochrome P450 enzymes in the liver, such as the CYP34A isozyme, can be affected by drugs that act as inhibitors or inducers.[60] Calcium-channel blockers are substrates for CYP34A isozymes, and several β-blockers are substrates for CYP2D6 isozymes.[64,65] Another common mechanism of interaction involves the P-glycoprotein (P-gp), an efflux pump that enables the transport of drugs across cell membranes for excretion.[60] Substrates for P-gp include many anticancer therapies, digoxin, and calcium-channel blockers.[65]

Drug databases are frequently used to identify potentially harmful drug interactions, with reported sensitivities and specificities over 80%.[66-68] ►Fig. 4 shows the risk of bradycardia and bradyarrhythmia with drug–drug interactions between nodal blocking agents and anticancer therapies, including data from Lexi-Interact (Wolters Kluwer) and Micromedex (IBM Corporation).[69,70] Among conventional chemotherapies, cases of additive bradycardia have been reported from pharmacodynamic drug–drug interactions between thalidomide and β-blockers, particularly in elderly patients with cardiac comorbidities.[71,72] Further, many targeted agents such as TKIs are known to interact with medications that affect CYP3A4 metabolism, leading to the risk of pharmacokinetic drug–drug interactions with calcium-channel blockers in particular.[73,74] For example, there are moderate to severe interactions between calcium-channel blockers and the TKIs imatinib, nilotinib, or vemurafenib from the inhibition of CYP3A4-mediated
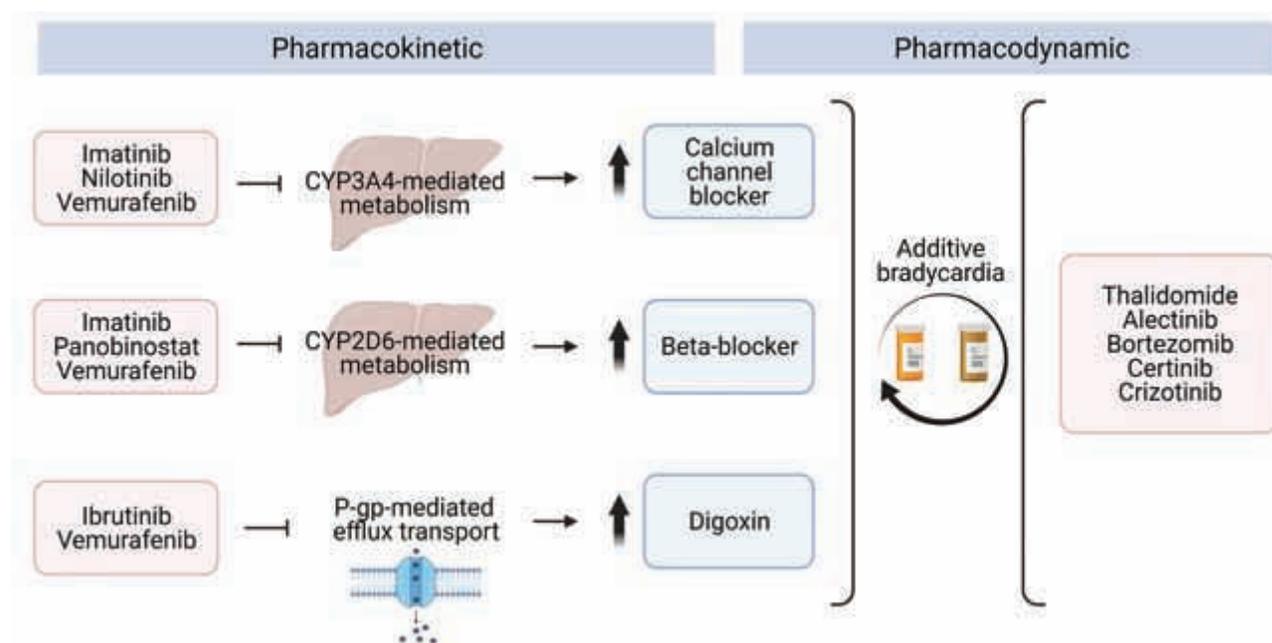

Fig. 4 *Drug–Drug interactions between anticancer and nodal blocking agents* (created by biorender.com).
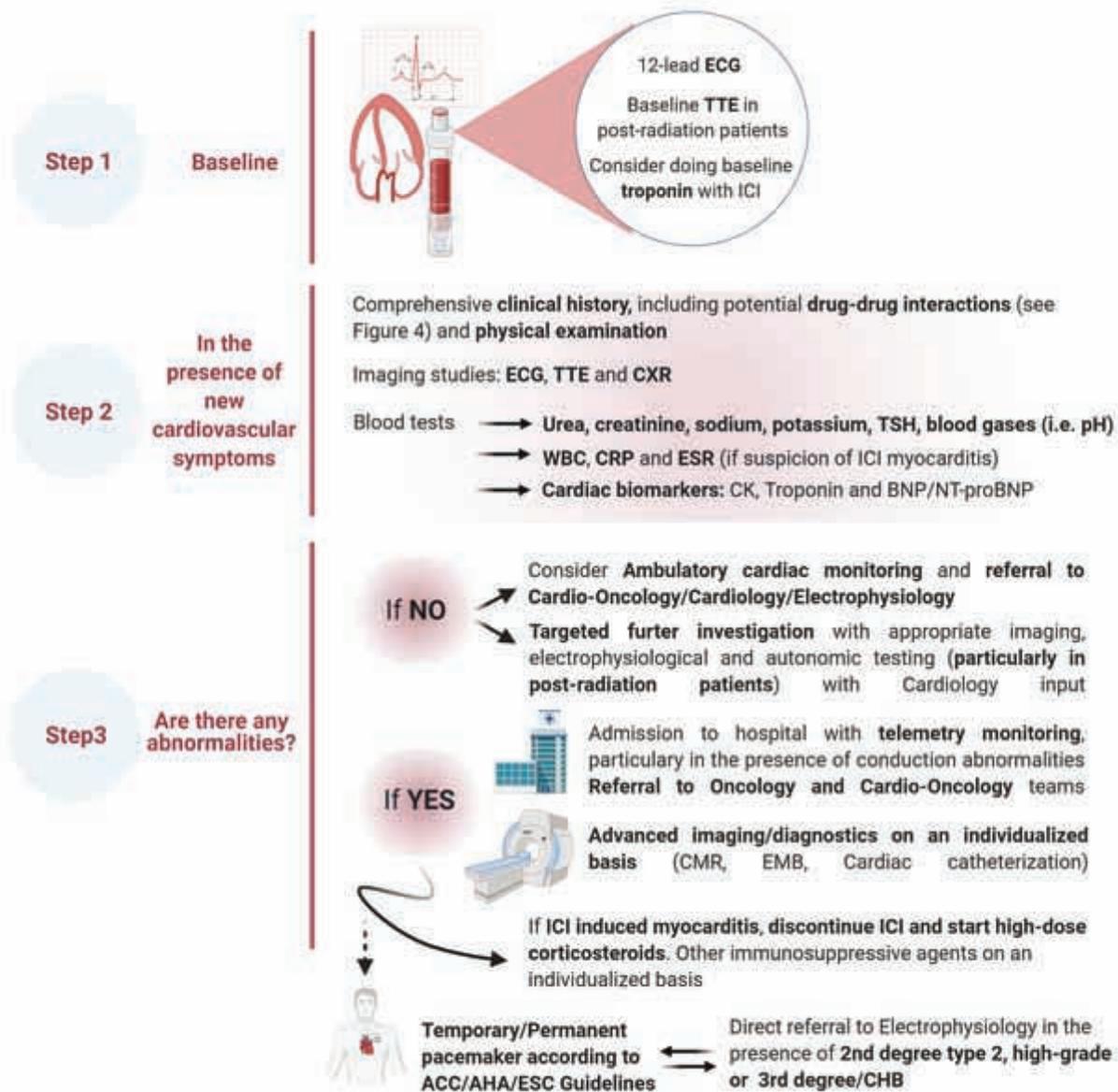
Fig. 5 *Proposed algorithm for the management of bradycardia/bradyarrhythmia, with a special focus on ICI- and radiation-induced conduction abnormalities*[49,97-100] (created by biorender.com). CK, creatine kinase; CMR, cardiac magnetic resonance; CRP, C-reactive protein; CXR, chest X-ray; ECG, electrocardiogram; EMB, endomyocardial biopsy; ESR, erythrocyte sedimentation rate; NT proBNP, N-terminal pro-brain natriuretic peptide; TTE, transthoracic echocardiography; WBC, white blood cell count.

metabolism leading to increased calcium-channel blocker concentration. Ibrutinib and vemurafenib, in particular, also have pharmacokinetic drug–drug interactions with digoxin due to P-gp-mediated digoxin efflux transport inhibition. Among histone deacetylase inhibitors, panobinostat has a minor pharmacokinetic interaction with metoprolol due to inhibition of CYP2D6-mediated metabolism. On the other hand, no formal pharmacokinetic drug–drug interactions have been conducted for nivolumab, pembrolizumab, and ipilimumab.[75-77] Further evaluation is needed to better define drug–drug interactions with nodal blocking agents and ICIs, especially given case reports of high-grade AVB in ICI-associated myocarditis.[40,48,78-80]

In reverse, nodal blocking agents can also potentiate anticancer therapies' concentration due to similar pharmacokinetic mechanisms. For example, doxorubicin, paclitaxel, vincristine, and vinblastine are P-gp substrates.[65] Thus, their drug concentrations can be increased in patients who are taking carvedilol, a moderate P-gp inhibitor. Similarly, diltiazem is a potent CYP3A4 inhibitor, and co-administration with CYP3A4 substrates such as doxorubicin, ibrutinib, busulfan, imatinib, vincristine, and vinblastine can increase the systemic concentration of such anticancer therapies.[60,64] For example, venetoclax exposure is increased with the concurrent use of both CYP3A4 inhibitors or P-gp inhibitors, such as carvedilol and diltiazem, that can result in increased

neutropenia and risk of tumor lysis syndrome. Alternative nodal blocking agents should be considered to avoid such chemotherapy toxicities.[81]

Diagnosis and Management

The American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) bradycardia clinical practice guidelines define a sinus rate <50 bpm and/or a sinus pause >3 seconds as potential components of sinus node dysfunction (SND). For the acute management of bradycardia related to moderate or severely symptomatic SND, symptomatic second- or third-degree AVB believed to be at the AV nodal level or any of the above resulting in hemodynamic compromise, atropine can be helpful to transiently increase sinus rate, and is a reasonable first step. If symptoms persist despite this and given atropine's short duration of action, β-adrenergic agonists such as isoproterenol, dopamine, dobutamine, or epinephrine may be considered to increase heart rate and/or improve AV conduction and/or symptoms. In the presence of symptoms or hemodynamic compromise refractory to medical therapy, temporary transvenous pacing is reasonable, and temporary transcutaneous pacing may be considered until a temporary transvenous, or permanent pacemaker is placed.[82] The need for temporary pacing is more likely when AV block is infra-Hisian.

There are no specific bradycardia-management guidelines produced by the European Society of Cardiology (ESC). Instead, there are guidelines related to cardiac pacing indications. They state that temporary transvenous pacing shall only be used in bradycardia refractory to positive chronotropic drugs. Temporary transvenous pacing should also be limited to cases of high-degree AVB without escape rhythm or life-threatening bradyarrhythmias.[83]

As per the ACC/AHA/HRS guidelines, for the management of bradycardia attributable to AVB in the chronic setting, such as the one related to radiation therapy, class I indications for permanent pacemaker implantation include Mobitz type II AVB, high-grade AVB, or CHB that is not attributable to reversible causes. For bradycardia attributable to SND, class I indication for permanent pacemaker implantation includes symptoms directly attributable to SND.[82] The ESC pacing guidelines recommend permanent pacemaker implantation (Class I recommendation) in patients whose symptoms are attributable to SND and patients with third- or second-degree type 2 AVB.[83]

►Fig. 5 represents a proposed algorithm for managing patients with cancer treatment-related bradycardia/bradyarrhythmia, with a special focus on ICI- and radiation-induced conduction abnormalities.

Future Directions

There is a limited body of literature regarding the true incidence of bradycardia and bradyarrhythmia related to chemotherapeutic agents, targeted molecular therapies, immunotherapies, and radiation. This is partially explained by the lack of systematic cardiac monitoring and reporting of arrhythmic events. In our view, a structured cardiac surveillance strategy with a homogenous classification of the arrhythmic events to be reported should be applied to clinical trials investigating the safety and efficacy of new cancer drugs. Databases/registries could also be established to obtain real-world quantitative data. Research of the possible mechanisms behind this type of cardiotoxicity is as well much needed. The already published evidence has mainly focused on arrhythmias in general, and there is a lack of data regarding the pathophysiology behind cancer drug-related bradycardia/bradyarrhythmia. Such knowledge could help develop evidence-based models to predict the patients who are more at risk of developing bradycardia/bradyarrhythmia and define the ones who may benefit from tighter monitoring strategies. Longer-term follow-up data are essential to determine the role of bradycardia on cancer patients' overall outcomes. In particular, in ICI-myocarditis patients presenting with CHB who frequently undergo pacemaker implantation, long-term data regarding the percentage of pacing would be helpful to evaluate the degree of temporal recovery of these conduction abnormalities if at all. The rapid advances in pharmacotherapy in oncology show no signs of abating and if we are to understand the nuances of the adverse effects of these drugs on the cardiovascular system then the future mandates much closer collaboration between cardiologists and oncologists to optimize patient outcomes.

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