ACOS Newsletter

www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal

Vol 1
Issue 4
Jan - March
2022

Table of Contents

We invite suggestions and contributions from our readers

Newsletter Designed by

KAVINACREATIONS

For any queries or suggestions, please send us an email on
indubansal@gmail.com or asiancardiooncologysociety@gmail.com

ACOS Newsletter

www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal

Vol 1
Issue 4
Jan - March
2022

Message from ACOS President (1/4)

Ibrutinib and Atrial Fibrillation
Dr Purvish M Parikh
Asian Cardio-Oncology Society President
Chief Advisor, MOC
Precision & Medical Oncologist, Asian Institute of Oncology, Mumbai

Ibrutinib, the first Bruton's tyrosine kinase (BTK) is licensed for use in and highly effective for treatment of B-cell haematological malignancies - chronic lymphocytic leukemia, mantle cell lymphoma, Waldenstrom's macroglobulinemia and marginal zone lymphoma. The phase 3 RESONATE study showed the ORR was 91% with ibrutinib and clinically valuable higher progression-free survival (44.1 months with ibrutinib vs 8.1 months with ofatumumab - $p<0.001$; hazard ratio [HR]: 0.148; 95% confidence interval [CI]: 0.113-0.196). This efficacy was also evident in high-risk patients (del(17p), TP53 mutation, del(11q), and/or unmutated IGHV status). Clearly a better overall survival (censored for crossover) with ibrutinib versus ofatumumab provided level 1 evidence in its favour. Interestingly, this advantage was with impressive safety - adverse events leading to discontinuation of ibrutinib in only 16% of patients. It was therefore reasonable to call RESONATE a landmark study.

In due course, studies of Ibrutinib started reporting cardiac adverse reactions – especially atrial fibrillations, bleeding, cardiac failure, hypertension and ventricular tachycardia. Of these, the first three had greater evidence. Still, historically TKIs that increased atrial fibrillation did not affect survival – and hence not much attention was paid to the data.

When second generation inhibitors (showing more selective BTK inhibion like acalabrutinib and zanubrutinib) were found to have lower cardiovascular side effects, interest perked up. The first real evidence was from the prospective study involving 53 patients with a B cell malignancy who received ibrutinib. Here systematic screening showed ibrutinib-related AF to be as high as 23% (95% CI 9–35%) at 12 months!

Additional studies showed that AF cardio-toxicity occurs via BTK-mediated pathway or via off-target pathways (the Tec non-receptor tyrosine kinase pathway) - both being expressed in cardiac tissue. Patients on Ibrutinib who develop AF have significantly lower cardiac PI3K-Akt activity and are predisposed to develop atrial fibrosis, that ultimately leads to AF. The final analysis of RESONATE study by Munir et al also added to our understanding. Over the 71 month follow up, grade ≥3 AEs included neutropenia (25%), pneumonia (21%), thrombocytopenia (10%), anaemia (9%), hypertension (9%), urinary tract infection (7%), diarrhea (7%), and atrial fibrillation (6%).

We will restrict our further discussion to Ibrutinib and AF only. Brijesh Patel and colleagues from West Virginia University showed that cancer patients treated with Ibrutinib had more Af and poorer survival.

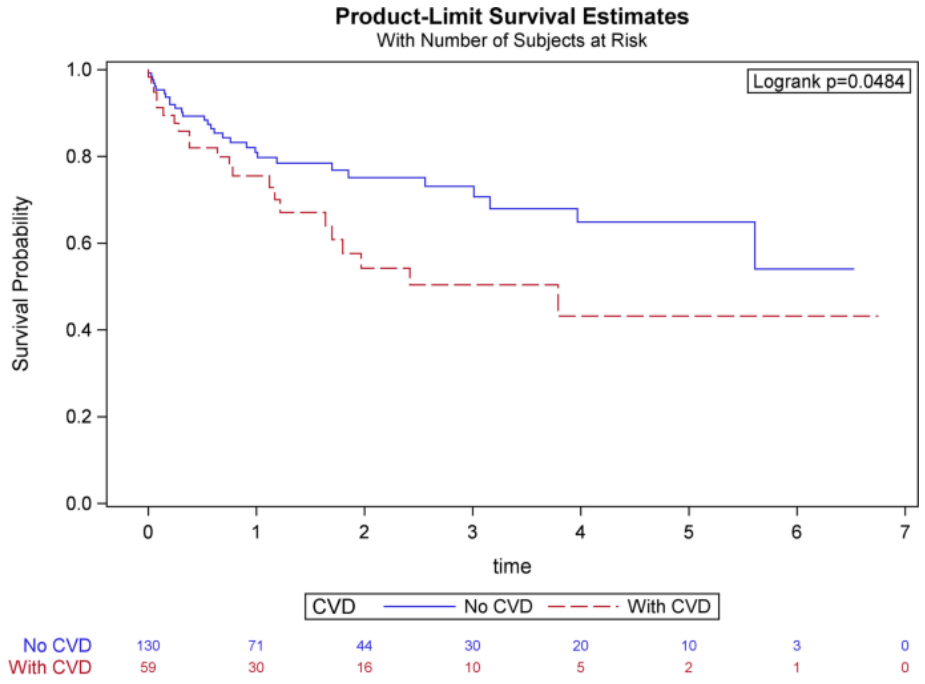
ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Message from ACOS President (2/4)

Patients were divided into those with pre-existing CVD (known history of coronary artery disease, heart failure, pulmonary hypertension, moderate valvular heart disease, and cardiovascular device implantation) and those without. In the 217 patients in the study, new-onset atrial arrhythmia was 17 % in those with pre-existing CVD arm and 7% in those without CVD (p = 0.02). Patients with pre-existing CVD also had lower survival (43% vs 54%, p = 0.04).

Figure 1: Survival probability amongst cancer patients treated with ibrutinib – with and without pre-existing cardiovascular disease (Reproduced from Avalon JC, Fuqua J, Miller T, Deskins S, Wakefield C, King A, Inderbitzin-Brooks' S, Bianco C, Veltri L, Fang W, Craig M, Kanate A, Ross K, Malla M, Patel B. Pre-existing cardiovascular disease increases risk of atrial arrhythmia and mortality in cancer patients treated with Ibrutinib. Cardiooncology. 2021 Nov 19;7(1):38. doi: 10.1186/s40959-021-00125-8. PMID: 34798905; PMCID: PMC8603583.)



We therefore recommend the following:

1. All cancer patients given ibrutinib therapy, should undergo evaluation for pre-existing cardiovascular risk factors and morbidity.

2. If pre-existing cardiovascular disease does exist

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Message from ACOS President (3/4)

a. Their treatment should be optimized as appropriate

b. Their cardiac monitoring should be increased (every three months or as appropriate) – particularly during the first year of therapy.

i. Physical pulse

ii. Electrocardiography

3. Remember that AF occurs paroxysmally - without systematic screening, the occurance might be missed or underestimated.

4. In case of any concern, doubt or red flags - Ibrutinib may need to be dose reduced or discontinued on case-to-case basis.

5. Even amongst patients without pre-existing cardiovascular disease, the risk of ibrutinib associated AF is higher than in cancer patients not on ibrutinib.

Suggested Reading:

1. Parikh Purvish M, Aggarwal Bansal Indu, Daddi Anuprita, Prem NN, DSouza Hollis et al: Ibrutinib and Atrial Fibrillation as Cardio Toxicity – A new safety warning that impacts overall survival. International Journal of Molecular and Immuno Oncology, 2022, in press

2. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, Bartlett NL, Brander DM, Barr PM, Rogers KA, Parikh SA, Coutre S, Hurria A, Brown JR, Lozanski G, Blachly JS, Ozer HG, Major-Elechi B, Fruth B, Nattam S, Larson RA, Erba H, Litzow M, Owen C, Kuzma C, Abramson JS, Little RF, Smith SE, Stone RM, Mandrekar SJ, Byrd JC. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018;379(26):2517–2528. doi: 10.1056/nejmoa1812836. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

3. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Kipps TJ, Moreno C, Montillo M, Burger JA, Byrd JC, Hillmen P, Dai S, Szoke A, Dean JP, Woyach JA. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019 Dec;94(12):1353-1363. doi: 10.1002/ajh.25638. Epub 2019 Oct 13. PMID: 31512258; PMCID: PMC6899718.

4. Khalid S, Yasar S, Khalid A, Spiro TP, Haddad A, Daw H. Management of Atrial Fibrillation in Patients on Ibrutinib: A Cleveland Clinic Experience. Cureus. 2018 May 29;10(5):e2701. doi: 10.7759/cureus.2701. PMID: 30062075; PMCID: PMC6063389.

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

Message from ACOS President (4/4)

5. Syed YY. Zanubrutinib: first approval. Drugs. 2020;80(1):91–97. doi: 10.1007/s40265-019-01252-4. [PubMed] [CrossRef] [Google Scholar]

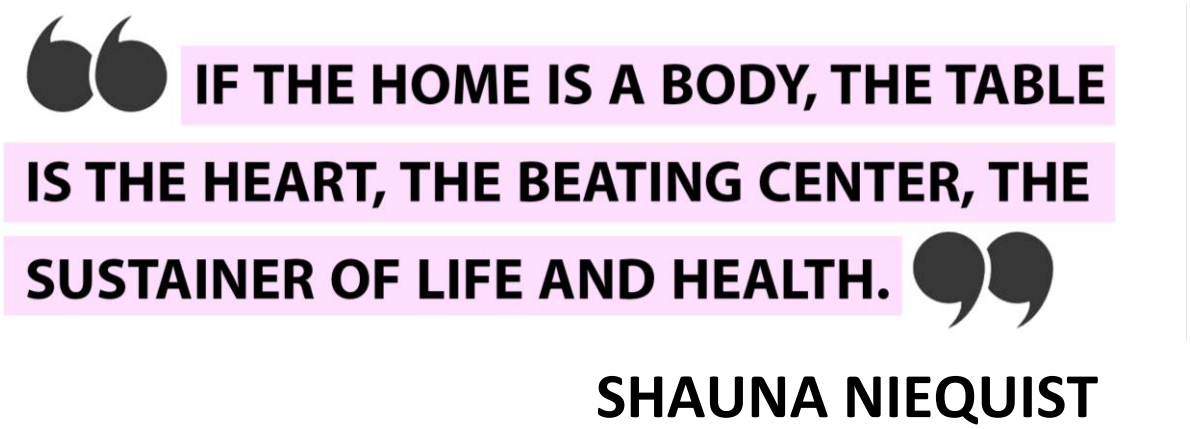
6. Sestier M, Hillis C, Fraser G, Leong D. Bruton's tyrosine kinase Inhibitors and Cardiotoxicity: More Than Just Atrial Fibrillation. Curr Oncol Rep. 2021 Aug 3;23(10):113. doi: 10.1007/s11912-021-01102-1. PMID: 34342738; PMCID: PMC8330192.

7. McMullen JR, Boey EJH, Ooi JYY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124(25):3829–3830. doi: 10.1182/blood-2014-10-604272. [PubMed] [CrossRef] [Google Scholar]

8. Packer DL,Lee K, Mascette AM, Bahnson TD, Mark DB, Monahan K, Rosenberg Y: Treatment of AFib: Is Ablation That Good or is Drug Therapy That Bad? https://www.acc.org/latest-in-cardiology/articles/2014/07/18/15/17/treatment-of-afib-is-ablation-that-good-or-is-drug-therapy-that-bad

9. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL; CABANA Investigators. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients with Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA. 2019 Apr 2;321(13):1261-1274. doi: 10.1001/jama.2019.0693. PMID: 30874766; PMCID: PMC6450284.

10. Avalon JC, Fuqua J, Miller T, Deskins S, Wakefield C, King A, Inderbitzin-Brooks' S, Bianco C, Veltri L, Fang W, Craig M, Kanate A, Ross K, Malla M, Patel B. Pre-existing cardiovascular disease increases risk of atrial arrhythmia and mortality in cancer patients treated with Ibrutinib. Cardiooncology. 2021 Nov 19;7(1):38. doi: 10.1186/s40959-021-00125-8. PMID: 34798905; PMCID: PMC8603583.



ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Toxicity and Cancer Treatment (1/14)

Dr Sayan Paul
Senior Consultant Radiation Oncologist
Apollo Multispeciality hospitals, Kolkata

Introduction: In the last two decades, new cancer therapies and drugs have significantly improved the survival of cancer patients. As survival improves normal tissue toxicities and quality of life become more and more important. Cardiac toxicity is an important factor for the quality of life of cancer patients and their survival. Sometimes cardiac toxicity becomes a more important cause of reduced survival than the malignancy itself. (1) Local radiation therapy and some systemic treatments are associated with significant cardiac toxicity. As we are getting newer weapons in our armamentarium, we need to be very cautious about their cardiac side effects. Cancer therapies with known cardiac toxicity include anthracyclines, biologic agents such as trastuzumab, and multikinase inhibitors such as sunitinib. Cardiac toxicity can result in different clinical manifestations including arrhythmias, myocardial ischemia, hypertension, acute heart failure (HF), and late-onset ventricular dysfunction with reduced (dilated cardiomyopathy) or preserved ejection fraction. (2) Among these presentations, dilated cardiomyopathy presents the poorest prognosis, especially if refractory to conventional HF therapy, with two-year mortality of 60%. (2)(3). Local radiotherapy for thoracic malignancy can also cause significant cardiac toxicity if not carefully planned to reduce the cardiac dose. Although the term “cardiotoxicity” generally refers to heart damage as a result of treatment, specifically, this has been used most commonly to describe left ventricular (LV) systolic dysfunction and heart failure (HF) related to certain types of chemotherapy. (4,5,6). As more and more data are being published it is now well known, that the risk of developing cardiovascular disease (CVD) is significantly higher in breast cancer patients treated with radiotherapy [7] Especially in left-sided breast cancer, the dose to the heart is approximately two or three times higher than in right-sided breast cancer [8]. Frequently, the apex of the heart is close, or even within the radiation field, resulting in a maximum dose exposure of the heart of up to > 20Gy [9]. Cardiac toxicity can result in different clinical manifestations including arrhythmias, myocardial ischemia, hypertension, acute heart failure (HF), and late-onset ventricular dysfunction with reduced (dilated cardiomyopathy) or preserved ejection fraction. (10) Among these presentations, dilated cardiomyopathy presents the poorest prognosis, especially if refractory to conventional HF therapy, with two-year mortality of 60%. (11)

Treatment and drugs notorious for the heart:
Several classes of drugs result in surprisingly high rates of cardiac adverse events. Cancer therapy-related cardiac dysfunction results in 2–3 % rates of symptoms in randomized trials and up to 26 % in observational studies [12]. At present, cardiotoxicity has been observed from the anthracyclines, monoclonal antibodies, tyrosine kinase inhibitors, proteasome inhibitors, anti-angiogenesis agents, and most recently some of the checkpoint immunotherapy agents. The mechanisms of cardiac toxicity though have been understood for only a few of them.

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Toxicity and Cancer Treatment (2/14)

Whereas radiation to thoracic malignancies mainly left-sided breast, chest wall, esophagus, lung tumours, or in some nodal irradiation can significantly increase heart dose and can cause significant cardiac side effects.

Baseline risk assessment for cardiac toxicity:

Multiple factors can increase the probability of cancer treatment-induced cardiotoxicity. These factors include cumulative dose, age (extremes of age), radiotherapy of the left side of the chest, previous exposure to cardiotoxins, and co-administration of anthracyclines and trastuzumab. Cardiac risk factors including hypertension, dyslipidemia, smoking, and diabetes mellitus are also thought to be predictors of chemotherapy-related cardiac toxicity [13,14,15]. It remains unclear whether ethnicity is a risk factor, although there was one study that suggested that African-Americans may be at increased risk of cardiac toxicity of cancer therapy [16]

Mechanisms and types of cardiac toxicities

Anthracyclines cause cellular damage by free radical production, intercalation into DNA, and altered intracellular signaling. Anthracycline-induced cardiotoxicity involves cardiomyocyte histological changes, mitochondrial apoptosis, fibrin deposition, alterations in the left ventricular ejection fraction, and eventually systolic and/or diastolic heart failure. Early arrhythmias and myocarditis/pericarditis syndromes are rare and for which the mechanism is less clear. For drugs other than anthracyclines, the direct toxic effects on cardiomyocytes are generally less clear. Several lines of research implicate fibroblasts, lymphocytes, oxidative stress, pro-apoptotic signaling, calcium transport, stromal interactions, and mitochondrial apoptosis as some of the more likely explanations for cardiotoxicity [17]. Hypertension, arrhythmia, and coronary artery disease are the other leading cardiovascular complications of cancer therapy. The VEGF-acting drugs are well known to cause hypertension and microvascular changes. Arrhythmias are reported with anthracyclines, several of the small molecule inhibitors, taxanes, vinca alkaloids, platinum, arsenic, thalidomide, antimetabolites, and IL-2. The most common arrhythmia is atrial fibrillation although ventricular tachycardia is also well reported. The rates of arrhythmia are generally under 10 % for these classes of drugs, except intraperitoneal cisplatin which has been reported to cause atrial fibrillation in 18–32 % of patients [18]. Coronary artery disease has been the subject of much debate as cancer survivorship has improved over the last few decades. The largest datasets come from pediatric cancer survivors who are well followed after their cancer diagnoses and who seem to have increased rates of coronary artery disease. Also, the breast and prostate cancer patients, who are treated with hormone deprivation therapies for many years, appear to have slightly higher rates of coronary artery disease than the general population [19-21]. Finally, patients treated with other cancer therapies may experience increased rates of late coronary artery disease due to other
factors such as increased systemic inflammation either due to the underlying disease, the treatments, the stress of treatment, or perhaps even due to changes in the microbiome that accompany a cancer diagnosis and treatment.

Cardiac monitoring

There are many methods to detect subtle cardiac side effects in cancer patients undergoing therapy. Assessments include noninvasive imaging to estimate the change in LVEF, invasive cardiac catheterization, and invasive cardiac biopsy methods to determine histological changes in the myocardium [22,23]. The most common tool to measure cardiac function is echocardiography, though MRI and radionuclide

Cardiac Toxicity and Cancer Treatment (3/14)

imaging is also heavily used. Schwartz et al. [24] proposed guidelines for echocardiographic monitoring of cardiac function in anthracycline-treated patients. Schwartz et al. also recommended obtaining a baseline ejection fraction by equilibrium radionuclide imaging, with subsequent imaging studies before consideration of any additional doses. They also provided specific criteria for drug discontinuation based on interval change in LV function. Cardiotoxicity was defined as a decline of the LVEF of more than 10 % and to a level below 50 %. For patients with a baseline LVEF of less than 50 %, a significant change was defined as a decline of more than 10 % or to a level <30 %. The study recommended interval calculations of the LVEF before administration of 100 mg/m2 of doxorubicin. They recommend another assessment after the use of 250–300 mg/m2 and a third assessment after the use of 400 mg/m2 in patients with known cardiac risk factors. For the patients without any cardiac risk factors, then an echocardiogram needs to be performed only if the cumulative dose exceeds 450 mg/m2. The conservative suggestion from Schwartz et al. [24] was that anthracycline or trastuzumab should be discontinued if the decline in the LVEF is more than 10 % and the LVEF value decreases to a level below 50 %. The proposed guidelines suggest that patients with baseline LVEF<50 % should carefully weigh risk versus benefit before starting a potentially cardiotoxic agent. If the LVEF is <30 %, then cardiotoxic agents should not be considered at all. For patients with LVEF between 30 and 50 %, repeat cardiac assessment should be obtained before each cycle and therapy withheld for a decline approaching 10 % [24, 25].

Molecular markers for cardiac toxicity:

Biomarker screening for early detection of cardiotoxicity has been a major interest due to its promising roles in the early detection of cardiac events during chemotherapy treatment. Troponin increases due to cardiomyocyte damage and B-type natriuretic peptide (BNP) increases due to elevation of filling pressure are often observed in anthracycline-treated patients [26]. Troponin I (TnI) and BNP were used as screening measures along with imaging echocardiography in a recent prospective study [25]. The biomarkers were measured before and 24 h after each cycle, and cardiac imaging was performed at baseline and after completion of the chemotherapy course. Out of 109 patients, 11 (10.1 %) suffered cardiac events. All of these 11 patients had at least one BNP test value of more than 11 pg/ml before the occurrence of the cardiac event. Only three of the patients that developed cardiac events had LVEF decline. The authors suggested serial use of cardiac biomarkers for earlier detection of cardiac events [26,27].

Similarly, a multicenter cohort study of 78 breast cancer patients undergoing doxorubicin and trastuzumab therapy examined a series of eight biomarkers. The eight biomarkers were measured at baseline and every 3 months. The biomarkers included high-sensitivity cardiac troponin I (hs-cTnI), high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), growth differentiation factor 15 (GDF-15), myeloperoxidase (MPO), placental growth factor (PlGF), soluble FMS-like tyrosine kinase receptor-1 (sFlt-1) and galectin 3 (gal-3). The study observed that six out of the eight biomarkers increased as early as 3 months, while NT-pro-BNP and gal-3 did not. The observed increases persisted at 15 months. The study found that MPO, GDF-15, and gal-3 increased before a decline in LVEF [28]. Further biomarker development was the ultimate conclusion of this study. A smaller study of 19 patients with Her2-positive breast cancer was assessed by serial high-sensitivity troponin T (hs-TnT) levels [27]. The study population was divided into two groups: the first group represented nine patients that had a decline in the LVEF>5 % and the second group represented the rest of the study population that had

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Toxicity and Cancer Treatment (4/14)

LVEF decline <5 %. The hs-TnT level at six months was significantly higher in the first group than in the second group (11.0 ± 7.8 vs. 4.0 ± 1.4 pg/mL, p < 0.01). The hs-TnT level at 6 months had 78 % sensitivity and 80 % specificity for predicting a reduction in LVEF at 15 months [28, 29]. Finally, a prospective study of NT-proBNP was performed in 100 patients with breast cancer who were treated with anthracyclines, taxanes, and trastuzumab. The analysis revealed significant increases in the levels of the NT-proBNP (p = 0.0001) at 3 and 6 months which preceded the detection of LVEF decline by echocardiography. As with the studies above, further validation is needed before these biomarkers are ready for routine clinical use [26, 30].

Table 1. Biomarker of myocardial damage: cardiac troponins.

BIOMARKERS	MECHANISMS	MAIN FINDINGS	REF.
Troponins	Release after cardiomyocyte damage induced by various mechanisms: ischemia, inflammation or oxidative stress	**Anthracycline:** – cTnI elevation in 1/3 of patients treated; proportion increases with cumulative dose – In patients with cTnI level > 0.5 ng/mL, 33%, 27% and 25% of increases occur right after, at 12 hours and 24 hours after dose and predict LVEF decrease at 1 month – Patients with cTnI > 0.5 ng/mL have a significant reduction in LVEF persisting for 3–7 months, in contrast to patients with cTnI < 0.5 ng/mL who show a transient decrease in LVEF at 3 months followed by complete recovery at 7 months – cTnT levels during the first 90 days after therapy predict cardiotoxicity at 4 years of follow-up – cTnI > 0.08 ng/mL persisting 1 month after therapy is associated with 84% risk of cardiotoxicity compared to 37% when the elevation is transient. Absence of cTnI elevation early and 1 month after therapy is associated with only 1% risk **Anthracycline—adjuvant trastuzumab:** – cTnI elevation early after anthracycline therapy and at 3 months is an independent predictor of cardiotoxicity with a 17.6 times increased risk	26–32

Abbreviations: cTn, cardiac troponin; LVEF, left ventricular ejection fraction.

Taken from: Henri et al. The role of Biomarkers in Decreasing risk of Cardiac Toxicity after Cancer Therapy. Biomarkers in Cancer 2016:8(s2) 39–45 doi:10.4137/BiC.s31798

Table 2. Biomarker of elevated left ventricular pressure: natriuretic peptides

BIOMARKERS	MECHANISMS	MAIN FINDINGS	REF.
Natriuretic Peptides	Release in response to elevation in LV filling pressure and wall stress	**Anthracycline:** – Correlations between NT-pro-BNP level and cumulative dose – NT-pro-BNP levels during the first 90 days after therapy predict cardiotoxicity at 4 years of follow-up – BNP > 51.3 ng/L has a 83% sensitivity and 90% specificity for the detection of cardiotoxicity – HF symptoms are more common when BNP > 100 pg/mL during follow-up **Various HDC protocols:** – Patients with elevated NT-pro-BNP have higher risks of cardiac toxicity, HF progression and death – Persistently elevated NT-pro-BNP level at 72 hours is associated with LV systolic/diastolic dysfunction at 12 months of follow-up	30,33–36,41,42

Abbreviations: BNP, B-type natriuretic peptide; HDC, high-dose chemotherapy; LVEF, left ventricular ejection fraction.

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Toxicity and Cancer Treatment (5/14)

Taken from: Henri et al. The role of Biomarkers in Decreasing risk of Cardiac Toxicity after Cancer Therapy. Biomarkers in Cancer 2016:8(s2) 39–45 doi:10.4137/BiC.s31798

Table 3. novel biomarkers for prediction of cardiac toxicity

BIOMARKERS	MECHANISMS	MAIN FINDINGS	REF.
hs-CRP	Non-specific marker of inflammation	– Correlations between hs-CRP levels and LV mass, wall thickness and dimension in patients with acute lymphoblastic leukemia independently of exposure to anthracycline	30
IL-6 ROS TAOS MPO	Markers of inflammation and oxidative stress	– Correlations between increases in IL-6 and ROS and reduction of LV systolic function in anthracycline-treated patients	45
		– Decrease in TAOS correlates with anthracycline cumulative dose. Changes in antioxidant defense capacity might explain cardiotoxicity	46
		– Increase from baseline to 3 months in cTnI (HR = 1.38) and MPO (HR = 1.34) are associated with increased risk of cardiotoxicity following anthracycline, taxanes, and trastuzumab treatement	47
Fibrinogen vWF t-PA PAI-1 ICAM-1	Markers of endothelial dysfunction	– Testicular patients receiving cisplatin-based therapy have higher levels of fibrinogen, vWF, PAI-1 and t-PA compared to those who do not	49,50
		– Patients with a PAI-1 > 43 ng/mL have a higher risk of metabolic syndrome	
		– Patients treated by cisplatin have higher levels of ICAM-1 compared to those who are not	
FABP GPBB	Markers of early detection of myocardial ischemia and necrosis	– Higher FABP level 24 hours after anthracycline-based therapy predicts cardiac toxicity defined as LVEF ≤ 50%	51
		– Increased release of GPBB (>7.30 g/L) after anthracycline is considered a sign of acute subclinical cardiotoxicity	52
Neuregulin-1	Paracrine growth factor released by endothelial cells that binds to ErbB receptors promoting cell growth, survival and repair	– NRG-1/ErbB regulates anthracycline-induced myofilament injury, and increased susceptibility of myofilaments to anthracycline in the presence of ErbB may explain cardiotoxicity	54,55
		– Patients with greater decline in LVEF have higher NRG-1 level at baseline	

Abbreviations: FABP, fatty acid binding protein; GPBB, glycogen phosphorylase BB; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; LVEF, left ventricular ejection fraction; MPO, myeloperoxidase; NRG-1, neuregulin-1; PAI-1, plasminogen activator inhibitor; ROS, reactive oxygen species; TAOS, total antioxidant status; t-PA, tissue-type plasminogen activator; vWF, von Willebrand factor.

Taken from: Henri et al. The role of Biomarkers in Decreasing risk of Cardiac Toxicity after Cancer Therapy. Biomarkers in Cancer 2016:8(s2) 39–45 doi:10.4137/BiC.s31798

Interventions to be done to reduce cardiac toxicity:

European Society of Medical Oncology (ESMO) has recently published a very comprehensive guideline for cardiac disease and toxicity management during cancer treatment. This guideline contains all necessary evidence-based recommendations that a clinician needs to manage cardiac toxicities during cancer treatment, below are the ESMO recommendations (31)

Recommendation 1.1. Screening for known cardiovascular (CV) risk factors in patients with cancer is recommended; treatment of identified CV risk factors according to current guidelines is recommended [I, A].

Recommendation 1.2. Many types of cancer therapy, especially mediastinal and left-sided chest radiation and certain ChT and targeted agents, can substantially affect the heart and vascular system and it is recommended that CV safety be monitored [I, A].

Recommendation 1.3. Close and early collaboration between cardiologists, oncologists, hematologists and radiation oncologists is recommended to ensure lifelong CV health and to avoid unnecessary discontinuation of cancer therapy [III, A].

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Toxicity and Cancer Treatment (6/14)

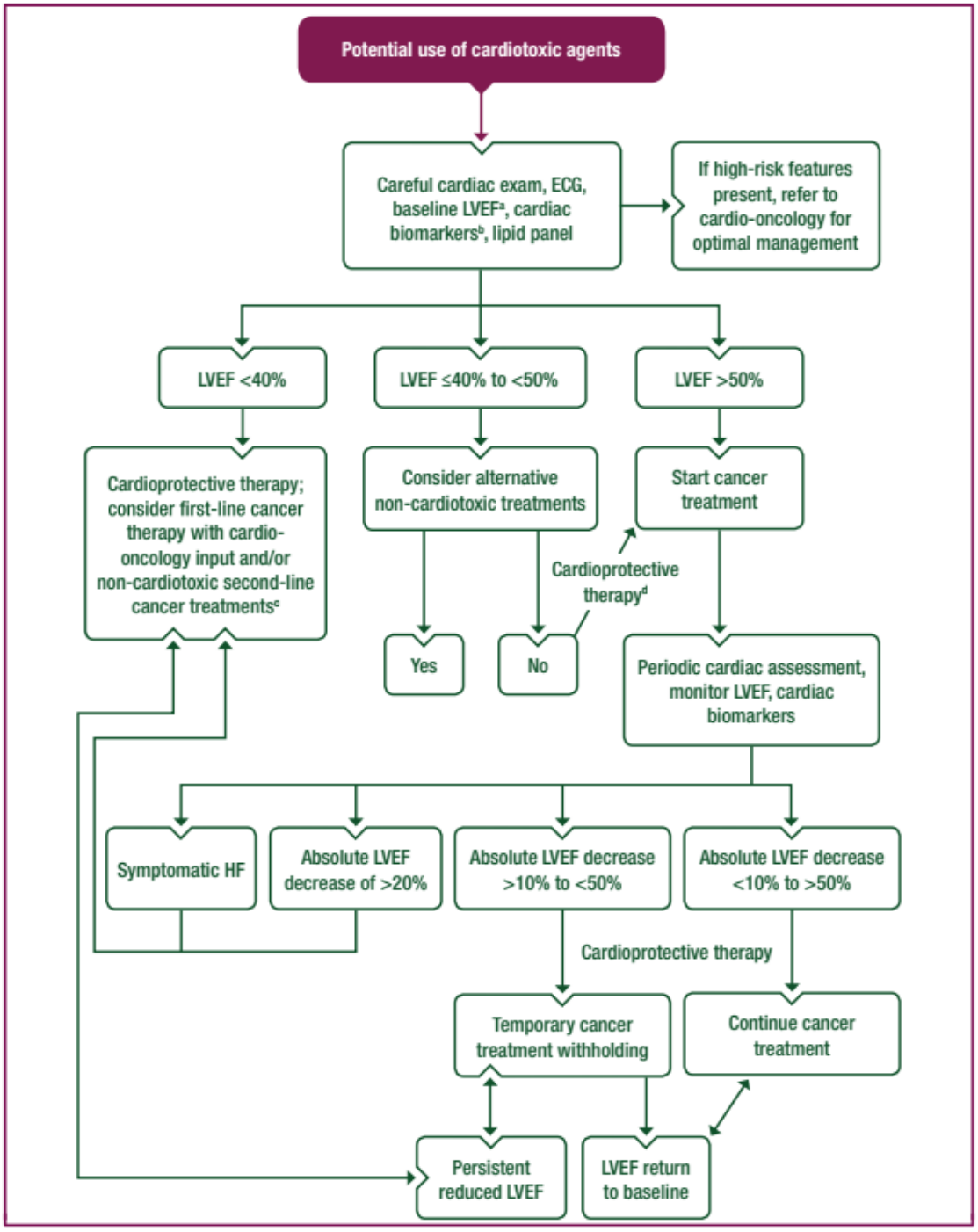


Figure 1. Proposed monitoring and management approach for patients undergoing potentially cardiotoxic anticancer therapy.

ECG, electrocardiogram; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction.

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Toxicity and Cancer Treatment (7/14)

a) LVEF assessment may include GLS as well if available.

b) Cardiac biomarkers include troponin and natriuretic peptides.

c) Under certain circumstances, if cardiotoxic therapy is the only viable option for anticancer treatment, it can be considered after close collaboration with cardio-oncology.

d) Cardioprotective therapy includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, carvedilol, spironolactone statin.

Recommendation 2.1. Routine use of cardiac biomarkers [hs-cardiac troponins (TnI or TnT), BNP or NT pro-BNP] for patients undergoing potentially cardiotoxic ChT is not well established. However, for high-risk patients (with preexisting significant CVD) and those receiving high doses of cardiotoxic ChTsuch as anthracycline, baseline measurement of such cardiac biomarkers should be considered [III, A].

Recommendation 2.2. For patients with a cancer diagnosis that requires treatment with a potentially cardiotoxic treatment, a baseline ECG, including measurement of heart rate QTc, is recommended [I, A].

Recommendation 2.3. In patients scheduled to undergo anticancer therapy associated with HF or LVD, a baseline evaluation of LVEF and diastolic function according to accepted comprehensive imaging practice is recommended [I, A].

Table 2. Classes of cardiovascular therapeutics that have some clinical trial evidence to suggest cardioprotection during anticancer therapy[a]

Class of CV therapy	Examples
ACE-I	Enalapril
ARB	Candesartan
MRA	Spironolactone
Statin	Pravastatin (many statins) Atorvastatin
Iron chelation/topoisomerase II inhibitor	Dexrazoxane
Antiplatelet	Aspirin
Anticoagulant	Enoxaparin Rivaroxaban/apixaban
BB	Carvedilol Nebivolol
Combination of ACE-I/BB	Enalapril Carvedilol

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CV, cardiovascular; MRA, mineralocorticoid receptor antagonist.
a Cardioprotection: any evidence that indicates the medication attenuates any CV dysfunction that may occur with potential cardiotoxic anticancer therapy.

Recommendation 3.1. In patients with a normal LVEF and CV risk factors who are scheduled to undergo anticancer therapy with known cardiotoxic agents, particularly those exposed to multiple cardiotoxic

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

Cardiac Toxicity and Cancer Treatment (8/14)

agents, prophylactic use of ACE-Is or ARBs (if intolerant to ACE-Is) and/or selected BBs may be considered to reduce the development of cardiotoxicity [II, B]. Dexrazoxane has been validated as a primary prevention cardioprotectant in selected populations who are receiving >300 mg/m2 anthracycline-based ChT, though not widely used due to its potential risk of reducing the efficacy of anthracyclines [II, C]. In patients with pre-existing cardiomyopathy, who require anthracycline-based ChT, concomitant administration of dexrazoxane from the beginning of anthracycline therapy can be considered regardless of the type of cancer [III, C].

Recommendation 3.2. Patients with evidence of hyperlipidaemia may benefit from treatment during active anticancer therapy, especially cardiotoxic ChT [II, C]

Recommendation 4.1. The following general principles are recommended for medical imaging in patients with cancer at risk for cardiac complications, particularly for the
periodic assessment of LV systolic function:

4.1(a) Highly reproducible, quantitative volumetric, nonirradiating imaging with quality control is recommended (quantitative 2D/3D echocardiography and CMR imaging
provide these characteristics) [I, A]
4.1(b) For each patient, the same imaging modality at the same facility is recommended for serial testing [I, A].
4.1(c) LV GLS imaging may be considered, when available, for baseline and serial monitoring of LV systolic function [III, C].

Recommendation 4.2. Asymptomatic patients with normal LVEF receiving anthracycline treatment should undergo surveillance for risk stratification and the early detection of cardiac toxicity consisting of the following:
4.2(a) Periodic (every 3-6 weeks or before each cycle) measurement of troponin I or troponin T, BNP or NT pro-BNP (if these biomarkers are available), using the same institutional laboratory, with an acceptable 99%
upper limit of normal reference range being the threshold for abnormal [III, C].
4.2(b) Reassessment of LV function following the general imaging principles is recommended after a cumulative dose of doxorubicin 250 mg/m2 or its equivalent anthracycline, after approximately each additional 100 mg/m2 (or approximately epirubicin 200 mg/m2) beyond 250 mg/m2 and at the end of therapy, even if <400 mg/m2 [I, A]

Recommendation 4.3. Aligned to the current recommendation by the FDA for asymptomatic non-metastatic patients undergoing adjuvant trastuzumab treatment, routine surveillance consisting of cardiac imaging every 3 months should be considered for the early detection of cardiac toxicity. However, the effectiveness of this strategy in patients at low CV risk, with no early evidence of LVD, has not been demonstrated and conversely high-risk patients may require closer monitoring [II, B].

Recommendation 4.4. Cardiac biomarker assessment may be considered as a valuable tool for cardiac safety surveillance in patients receiving adjuvant anti-HER2-based treatment [III, C].

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Toxicity and Cancer Treatment (9/14)

Recommendation 4.5. Asymptomatic patients undergoing anti-HER2-based treatment of metastatic disease should have general surveillance for CV toxicity that may consist of periodic cardiac physical examination, cardiac biomarkers and/or cardiac imaging [I, B].

Recommendation 4.6. For patients receiving cancer therapeutics associated with a risk of systemic HTN, especially anti-VEGF-based therapy, establishment of a baseline BP measurement and serial BP monitoring is recommended along with surveillance for the early detection of CV toxicity that may consist of periodic cardiac physical examination, cardiac biomarkers and/or cardiac imaging [I, A].

Recommendation 5.1. In asymptomatic patients undergoing treatment with anthracyclines, with an LVEF decrease of 10% from baseline to 50%, or a decrease in LVEF to 40% but <50%, the following evaluations are recommended: Cardiology consultation (preferably a cardio-oncology specialist). Consider initiation of cardioprotective treatments (ACEIs, ARBs and/or BBs), if not already prescribed. A statin may be considered if concomitant coronary disease is present. Consider cardiac biomarkers (BNP or NT-proBNP and TnI or Tnt) and a cardiac-focused physical exam after each dose of anthracycline. Repeat LVEF assessment after alternate doses of anthracycline-based ChT. If further anthracycline-based ChT is planned, the benefit-risk assessment of continued anthracycline use as well as options of non-anthracycline regimens should be discussed, and the use of dexrazoxane and/or liposomal doxorubicin should be considered [III, A].

Recommendation 5.2. In asymptomatic patients undergoing treatment with trastuzumab, with an LVEF decrease of 10% from baseline or a drop in LVEF to 40% but <50%, the following evaluations are recommended: Cardiology consultation, preferably a cardio-oncology specialist. Consider initiation of cardioprotective treatments (ACEIs, ARBs and/or BBs), if not already prescribed. Consider cardiac biomarkers (BNP or NT-pro BNP and TnI or Tnt) monthly and periodic cardiac-focused physical exams for ongoing monitoring of cardiac toxicity. If trastuzumab is stopped, repeat LVEF within 36 weeks, and resume trastuzumab therapy if LVEF has normalised to >50%.
It is possible that trastuzumab therapy may be continued with mild asymptomatic reductions in LVEF [III, A].

Recommendation 5.3. In asymptomatic patients undergoing treatment with any cardiotoxic anticancer therapy, with normal LVEF but a decrease in average GLS from baseline assessment (12% relative decrease or 5% absolute decrease), the following evaluations/treatments should be considered: Consider initiation of cardioprotective treatments (ACEIs, ARBs and/or BBs) if not already administered. Repeat LVEF/strain measurement every 3 months unless a cardiac physical exam is required or symptoms develop (if this occurs, LVEF/strain should be repeated with suspected cardiac toxicity).
Life-saving ChT should not be altered solely based on changes in LV strain [III, B].

Recommendation 5.4. In asymptomatic patients undergoing treatment with cardiotoxic anticancer therapy and an elevation in cardiac troponin, the following measures should be considered: Cardiology consultation, preferably a cardio-oncology specialist. Consider LVEF and GLS assessment with echocardiography. Appropriate evaluation to exclude ischaemic heart disease as a comorbidity. Consider initiation of cardioprotective treatments (ACEIs, ARBs and/or BBs), if not already prescribed. Consider initiation of dexrazoxane in patients undergoing anthracycline-based ChT. It is possible that anticancer

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

Cardiac Toxicity and Cancer Treatment (10/14)

therapy may be continued without interruption if only mild elevations in cardiac biomarkers occur without significant LVD [III, C]

Recommendation 6.1. In patients with an abnormal LVEF <50% but >40%, medical therapy with an ACE-I, ARB and/or BB is recommended before potential cardiotoxic treatment [I, A].

Recommendation 6.2. For those with an LVEF <40%, anthracycline therapy, in particular, is not recommended unless there are no effective alternative anticancer treatment options [IV, A].

Recommendation 6.3. For a patient undergoing treatment with any cardiotoxic agent presenting with unexplained signs and symptoms such as (but not limited to) sinus tachycardia, rapid weight gain, dyspnoea, peripheral oedema or ascites, obtaining a cardiology consultation, reassessing of LVEF and potentially measuring cardiac biomarkers is recommended [III, A].

Recommendation 6.4. For a patient undergoing treatment with trastuzumab (or any HER2-targeted molecular therapy) with signs and symptoms of HF, or an asymptomatic patient with an LVEF <40%, the same assessments as those for an LVEF <40% are recommended. In addition, trastuzumab (or any HER2-based therapy) should be withheld until the cardiac status has stabilised. A discussion regarding the risks and benefits of continuation should be held with the multidisciplinary team and the patient [I, A].

Recommendation 6.5. For a patient in whom trastuzumab therapy (or any HER2-targeted molecular therapy) has been interrupted, whose LVEF is >40% and/or whose signs and symptoms of HF have resolved, resumption of trastuzumab therapy should be considered, supported by:
Continued medical therapy for HF and ongoing cardiology care.
Periodic cardiac biomarker assessments.
Periodic LVEF assessments during ongoing treatment [III, B].

Recommendation 6.6. For a patient in whom trastuzumab therapy (or any HER2-targeted molecular therapy) has been interrupted, whose signs and symptoms of HF do not resolve and/or LVEF remains <40%, resumption of trastuzumab therapy may be considered if no alternative therapeutic option exists. The risk-benefit assessment of prognosis from cancer versus HF should be discussed with the multidisciplinary team and the patient [IV, C]. Recommendation 6.7. For a patient undergoing treatment with sunitinib (or other anti-VEGF-based therapy), who shows signs and symptoms of HF, assessment and optimization of BP control is recommended and measurement of LVEF and/or cardiac biomarkers should be considered. In addition, sunitinib (or other anti-VEGF-based therapies) should be interrupted. The patient should be assessed to determine whether reinstituting those therapies is appropriate [III, A].

Recommendation 7.1. For asymptomatic patients who have been treated with cardiotoxic agents and have normal cardiac function, periodic screening for the development of new asymptomatic left ventricular dysfunction with cardiac biomarkers and potentially cardiac imaging should be considered at 6-12 months, at 2 years post-treatment and possibly periodically thereafter [III, B].

Recommendation 7.2. For patients who developed LVD or HF due to trastuzumab (or any HER2-targeted molecular therapy), anthracyclines or other anticancer therapies, CV care including medical treatment

Cardiac Toxicity and Cancer Treatment (11/14)

with ACE-Is, ARBs and/or BBs and regular cardiology review (e.g., annual if asymptomatic) should be continued indefinitely, regardless of improvement in LVEF or symptoms. Any decision to withdraw HF-based therapy should only be done after a period of stability, no active cardiac risk factors and no further active anticancer therapy [III, B].

Recommendation 7.3. For patients with a history of mediastinal chest RT, evaluation for CAD and ischaemia, as well as valvular disease is recommended, even if asymptomatic, starting at 5 years post-treatment and then at least every 3e5 years thereafter [I, A].

Recommendation 7.4. Patients undergoing anticancer therapy and long-term cancer survivors should be encouraged to exercise on a regular basis [III, B].

Recommendation 7.5. Patients undergoing anticancer therapy and long-term cancer survivors should be encouraged to have healthy dietary habits (high intake of fresh fruits/vegetables and whole grains as compared with refined grains, processed and red meats and high-fat foods) and to maintain a normal weight [IV, B].

Immune checkpoint inhibitor-associated CV toxicity: There has been a revolution in cancer therapy over the past 5-10 years in which previously resistant malignancies are effectively treated with immune-based therapies known as immune checkpoint inhibitors (ICIs). In general, these therapies are remarkably well tolerated and highly effective across a number of malignancies. In fact, several professional societies have established current recommendations regarding ICI therapy, though the evidence and strength of recommendations for the management of CV toxicity as part of these guidelines is preliminary and relatively scant in practical detail. At present time, there are several clinical reports that inform the current recommendations. As such, these recommendations are formulated based on mostly expert opinion from a few prospective observational studies, case series and/or retrospective data analyses.

Recommendation 8.1. For patients who develop new CV symptoms or are incidentally noted to have any arrhythmia, conduction abnormality on ECG or LVSD on echocardiogram, while undergoing (or after recent completion) of ICI therapy, further appropriate work-up (ECG, troponin, BNP or NT-pro-BNP, C-reactive protein, viral titre, echocardiogram with GLS, cardiac MRI) for ICI-associated CV toxicity, particularly myocarditis and other common differential diagnoses should be carried out promptly [IV, C].

Recommendation 8.2. Endomyocardial biopsy for diagnosis should be considered if the diagnosis is highly suspected with otherwise negative work-up [IV, C].

Recommendation 8.3. With either suspicion or confirmation of ICI-associated myocarditis, further therapy with ICIs should be withheld and high-dose corticosteroids (methylprednisolone 1000 mg/day followed by oral prednisone 1 mg/kg/day) should be initiated promptly. Corticosteroids should be continued until resolution of symptoms and normalisation of troponin, LV systolic function and conduction abnormalities [IV, C].

Recommendation 8.4. For steroid-refractory or high-grade myocarditis with haemodynamic instability, other immunosuppressive therapies such as anti-thymocyte globulin, infliximab (except in patients with

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

Cardiac Toxicity and Cancer Treatment (12/14)

HF), mycophenolate mofetil or abatacept should be considered [IV, C].

Recommendation 8.5. For patients with cardiomyopathy and/or HF, appropriate guideline-directed medical therapy and hemodynamic support should be provided as indicated [IV, C].

Recommendation 8.6. For patients with atrial or ventricular tachyarrhythmia or heart block, appropriate medical and supportive care should be provided as indicated [IV, C].

Recommendation 8.7. ICI therapy should be permanently discontinued with any clinical myocarditis. The decision regarding restarting ICI therapy in the absence of alternative available antineoplastic therapy needs to be individualized with multidisciplinary discussion considering the cancer status, response to prior therapy, the severity of cardiotoxicity, regression of toxicity with immunosuppressive therapy and patient preference after weighing the risks and benefits. If ICI therapy needs to be restarted, monotherapy with an anti-programmed cell death protein 1 (anti-PD-1) agent might be considered with very close surveillance for cardiotoxicity development [V, C]

Conclusion: As cardiac toxicity is a major concern with anti-cancer treatment a close liaison with cardiology colleagues is of utmost importance. Proper risk assessment, individualized treatment planning based on cardiac comorbidities and risks is the key to minimize cardiac morbidity and mortality. For systemic treatment cardioprotective drugs should be used, when necessary, dose modification of systemic therapy drugs may be required. Sometimes stoppage of the concerned drug may be unavoidable if the risk outweighs benefits.In case of left-sided thoracic radiation heart dose should kept under recommended constraints with all possible mechanisms possible. More conformal treatment planning, intensity modulation, deep inspiratory breath-holding technique, and use of proton beam or other particle therapy should be considered to reduce radiation-induced cardiac toxicities. More research should be encouraged to generate meaningful data which can guide the clinician to reduce cardiac side effects without compromising the intensity of cancer-directed treatment to get the best result both in terms of cancer control and minimizing cardiac toxicities.

References:

1. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009; 53(24):2231–2247.

2. Bonow RO, Bennett S, Casey DE Jr, et al. ACC/AHA Clinical Performance Measures for Adults with Chronic Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures): endorsed by the Heart Failure Society of America. Circulation. 2005;112(12):1853–1887.

3. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342(15):1077–1084.

4. Lenihan DJ, Cardinale D, Cipolla CM. The compelling need for a cardiology and oncology partnership and the birth of the International CardiOncology Society. Prog Cardiovasc Dis. 2010;53:88-93.

Cardiac Toxicity and Cancer Treatment (13/14)

5. Hequet O, Le QH, Moullet I, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol. 2004;22:1864-1871.

6. van der Pal HJ, van Dalen EC, Hauptmann M, et al. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. Arch Intern Med. 2010; 170:1247-1255.

7. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987–98.

8. Taylor CW, Nisbet A, McGale P, et al. Cardiac exposures in breast cancer radiotherapy: 1950s–1990s. Int J Radiat Oncol Biol Phys. 2007;69(5):1484–95.

9. Taylor CW, Povall JM, McGale P, Nisbet A, Dodwell D, Smith JT, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. Int J Radiat Oncol Biol Phys. 2008;72:501–7

10. Bonow RO, Bennett S, Casey DE Jr, et al. ACC/AHA Clinical Performance Measures for Adults with Chronic Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures): endorsed by the Heart Failure Society of America. Circulation. 2005;112(12):1853–1887.

11. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342(15):1077–1084.

12. Thavendiranathan P, et al. Breast cancer therapy-related cardiac dysfunction in adult women treated in routine clinical practice: a population-based cohort study. J Clin Oncol. 2016;34(19): 2239–46

13. Von Hoff DD, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710–7

14. Zambetti M, et al. Long-term cardiac sequelae in operable breast cancer patients given adjuvant chemotherapy with or without doxorubicin and breast irradiation. J Clin Oncol. 2001;19(1): 37–43

15. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 2000;355(9217):1757–70.

16 Hasan S, et al. Doxorubicin cardiotoxicity in African Americans. J Natl Med Assoc. 2004;96(2):196–9

17 Geisberg CA, Sawyer DB. Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage. Curr Hypertens Rep. 2010;12(6):404–10.

18 Guglin M, et al. Introducing a new entity: chemotherapy-induced arrhythmia. Europace. 2009;11(12):1579–86.

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

Cardiac Toxicity and Cancer Treatment (14/14)

19. Curigliano G, et al. Cardiotoxicity of anticancer treatments:epidemiology, detection, and management. CA Cancer J Clin.2016. doi:10.3322/caac.21341.

20. Haque R, et al. cardiovascular disease after aromatase inhibitor use. JAMA Oncol. 2016. doi:10.1001/jamaoncol.2016.0429.

21. Khan NF, et al. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. Br J Cancer. 2011;105(Suppl 1):S29–37.

22. Cascales A, et al. Association of anthracycline-related cardiac histological lesions with NADPH oxidase functional polymorphisms. Oncologist. 2013;18(4):446–53.

23. Stoddard MF, et al. Prolongation of isovolumetric relaxation time as assessed by Doppler echocardiography predicts doxorubicin-induced systolic dysfunction in humans. J Am Coll Cardiol. 1992;20(1):62–9.

24. Schwartz RG, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med. 1987;82(6):1109-18.

25. Piotrowski G, et al. Role of echocardiography in monitoring of cardiac toxicity of cancer pharmacotherapy. Expert consensus statement of the Polish clinical forum for cardiovascular imaging. Kardiol Pol. 2014;72(6):558–75

26. Henri C, Heinonen T, Tardif JC. The role of biomarkers in decreasing risk of cardiac toxicity after cancer therapy. Biomark Cancer. 2016;8(Suppl 2):39–45.

27. Lenihan DJ, et al. The utility of point-of-care biomarkers to detect cardiotoxicity during anthracycline chemotherapy: a feasibility study. J Card Fail. 2016;22(6):433–8.

28. Putt M, et al. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. Clin Chem. 2015;61(9):1164–72.

29. Katsurada K, et al. High-sensitivity troponin T as a marker to predict cardiotoxicity in breast cancer patients with adjuvant trastuzumab therapy. Springerplus. 2014;3:620.

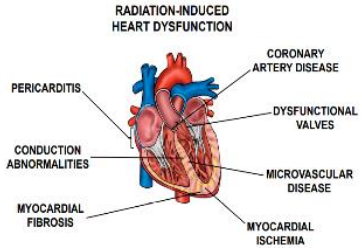
30. De Iuliis F, et al. Serum biomarkers evaluation to predict chemotherapy-induced cardiotoxicity in breast cancer patients. Tumour Biol. 2016;37(3):3379–87

31 G. Curigliano et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations: Annals of oncology VOLUME 31, ISSUE 2, P171-190, FEBRUARY 01, 2020

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Radiation Induced Heart Disease - Each Gray Matters (1/2)

Dr Arpana Shukla
Senior Consultant and Head Department of Radiation Oncology, Shalby Hospital, Indore



Cardiovascular and cancerous diseases are the leading causes of mortality worldwide. The most common adult malignancies are breast, lung, oesuphagus and head and neck. Recently due to significant improvement in management of cancer long term survival rates has improved. consequently, age related chronic diseases and cardiovascular risk factors including hypertension, diabetes hypertension, diabetes is often aggravated by chronic side effects of multimodality cancer therapy. cardiovascular disease is the leading cause of non-malignancy related death in cancer survivors.

Radiation therapy is one of the main modalities in multidisciplinary management of cancer. Basic aim of radiation therapy since century ago is to achieve a tumoricidal dose to the tumor at the same time protect the surrounding organs at risk (OAR) in order to achieve a cure with minimal complications. Heart is the OAR in treating various malignancies like Breast, oesophagus, lung and mediastinal lymphoma and thymoma. Exposure of the heart and surrounding vasculature to radiation may lead to several adverse structural and functional changes in the heart, collectively referred to as radiation-induced heart dysfunction (RIHD), including pericarditis, ischemic heart disease, conduction abnormalities, myocardial fibrosis, and valvular abnormalities. Cardiac myocytes are relatively resistant to radiation damage because of their postmitotic state. But endothelial cells remain sensitive to radiation, and the pathophysiology of most forms of RIHD appears to be associated with damage to endothelial cells. Risk factors for RIHD are Anterior or left chest irradiation, High cumulative dose of radiation (> 30 Gy) Younger age (< 50) at time of radiation therapy, High dose of radiation fractions (> 2 Gy/day), Presence and extent of tumor in or next to the heart, Inadequate or absent shielding, Concomitant chemotherapy (eg, anthracyclines) and Pre-existing cardiovascular disease and risk factors. Besides radiotherapy other treatments modality like chemotherapy, immunotherapy and targeted therapies also affects cardiac functions, hence pre-treatment cardiac assessment and thorough review of past treatment received is crucial.

Much of our current knowledge on radiation-induced cardiovascular complications in cancer survivors is based on the patients' data coming from the era of the 1980s or before that, with less developed RT techniques, extended RT fields, and high radiation doses. These side effects may present clinically months to years after RT, affecting patient quality of life and at times even leading to increased

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

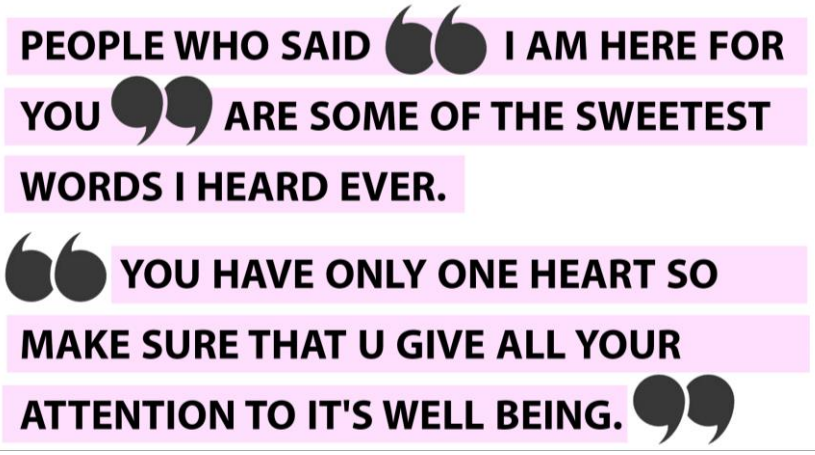
Radiation Induced Heart Disease - Each Gray Matters (2/2)

mortality. For example, patients who received tangential RT for left-sided breast cancer in the 1970s and 1980s had an increased risk for cardiovascular mortality at 15 years post-treatment. In patients that received mediastinal radiation for Hodgkin's disease in the 1960s–1990s, there was a higher prevalence of cardiac abnormalities. In addition, non-small cell lung cancer (NSCLC) patients may experience RIHD within two years of radiation exposure. RIHD is dose and volume dependent. The three major strategies employed to decrease cardiac exposure include reducing the radiation dose, reducing the radiation field and volume, and using newer planning and delivery techniques.

A number of advances in radiation oncology like IMRT, IGRT, VMAT, DIBH, GATING etc have made radiation delivery more precise and allow more effectively delivery of doses to the target volume while reducing the radiation doses to surrounding normal tissues. Proton therapy has more potential to improve therapeutic ratio but logistics remain the concern. However, numerous studies have shown that modern RT technology has not fully eliminated the risk of RIHD. In breast cancer patients, it has been estimated that there is an approximately 4–16% relative increase in heart disease and/or major coronary events for each 1 Gy in mean heart dose received. There is no safe dose. An independent association has been shown between the dose received by the left anterior descending artery (LAD) and RIHD, including myocardial infarction.

LONG TERM SURVIVAL OF H&N radiotherapy in particular should undergo regular ultrasound scans of the extracranial vessels supplying the brain to detect any atherosclerotic changes, since the incidence of carotid stenosis increases by 18 to 38% after radiotherapy for head and neck tumours compared to 0 to 9.2% in patients who did not receive radiotherapy. Consequently, cardiac risk factors should be monitored more intensively, and in cases involving severe carotid stenosis, angioplasty stenting or surgery should be discussed.

Long-term follow-up with regular screening for RIHD plays an important role in the management of cancer survivors who have undergone RT. depending on the individual risk profile. Cardiac oncology is emerging as a new speciality to deal with the cardiac issues in cancer patients.



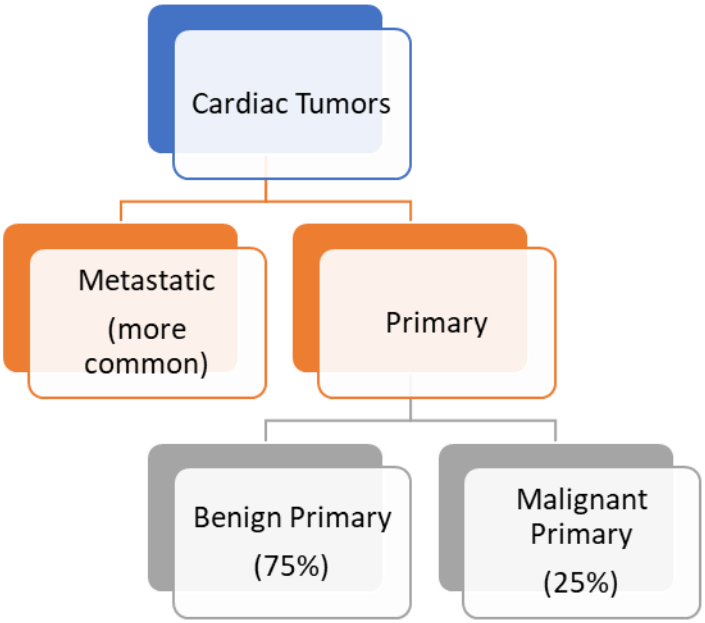
ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Tumors (1/4)

Dr Rachit Saxena
Senior Consultant, Cardiac and Aortic Surgery
Narayana Superspeciality Hospital, Gurugram

The heart remains an uncommon location for neoplastic growth. Analysis of several autopsy series shows the incidence to be around 0.02% (1). The neoplastic involvement of the heart occurs much more commonly as a metastatic growth rather than as a primary cardiac tumors. However among the primary cardiac tumors, benign cardiac tumors (75%) are much more common than malignant cardiac tumors (25%) (1).

Classification of Cardiac Tumors



Metastatic cardiac tumors

Metastatic involvement of cardiac tissue is 30-40 times more common. Cardiac secondaries of primary tumor can occur by means of hematogenous or lymphogenous spread (2). The following primary malignancies have a higher propensity to metastasise to the heart (3)

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Tumors (2/4)

1. Melanoma

2. Lung Carcinoma

3. Breast Carcinoma

4. Soft tissue sarcoma

5. Renal Cell carcinoma

6. Leukemia and Lymphoma

Cardiac secondaries are usually small and single or multiple solid deposits. The cardiac symptoms are usually uncommon and the clinical presentation is dominated by the symptoms pertaining to the primary tumor. The prognosis is also dependent on the primary (2). Surgical treatment of these secondaries is usually not possible because the deposits are multiple and often not confines only to the heart. However, surgical resection is considered if the tumor can be removed in toto (4).

Primary cardiac tumors

Primary cardiac tumors of the heart although far more uncommon but are mostly benign.

Benign Primary Cardiac Tumors

A) Myxoma – Cardiac Myxomas account for almost 70% of the primary cardiac tumors (5). Myxomas occur more frequently in women than in men and occur more commonly in the middle age group. The myxomas can occur in the left atrium (75%), the right atrium (20%) or rarely in the ventricle. They usually arise in the area of the fossa ovalis and are usually pedunculated, gelatinous structures which can grow large enough to protrude across the mitral valve into the left ventricle in each cardiac cycle during diastole and retract back into the left atrium during systole. These can cause obstruction to the flow of blood and thereby manifesting as stenotic valvular lesion or can cause damage to valves leading to valvular regurgitation and they also have potential to embolise so can manifest as vascular thromboembolic phenomenon.

B) Papillary Fibroelastoma – these are avascular papillomas and originate from the cardiac valvular tissue. These are more commonly located on the left sided valves – the mitral and the aortic valves. These usually have embolic manifestations rather than primary valvular dysfunction.

C) Rhabdomyomas – these are primarily encountered in infants and children and present as multiple deposits in the ventricular or septal musculature. These can grow in size causing obstructive symptoms or conduction abnormalities.

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Tumors (3/4)

D) Hemangiomas – Usually asymptomatic and incidentally detected.

E) Teratoma – are commonly seen in the pericardium of infants and children and may be attached to the great vessels causing obstructive symptoms

Malignant primary tumors

Most of the primary malignant lesions are sarcomas (6) which can grow in any of the cardiac chambers

A) Angisarcoma – Most common primary neoplasm originating from mesenchymal angioblasts. These infiltrate the myocardium and can rapidly cause cardiac failure due to extensive myocardial dysfunction.

B) Rhabdomyosarcoma - can be found in any cardiac chamber and originates from the striated cardiac muscle fibres. There is aggressive infiltration in to the cardiac musculature and also into the neighbouring structures - pericardium or the mediatinal structures.

C) Leiomyosarcoma - originates from cardiac smooth muscles.

D) Fibrosarcoma - originates from the fibroblasts of cardiac connective tissue.

Management of cardiac tumors

A) Surgical resection – a simple surgical resection of the tumor is possible in benign tumors like myxomas. After establishment of Cardiopulmonary bypass in the routine manner, the entire tumor is excised completely along with the tissue of origin. The resection may need to be accompanied with valvular reconstruction incase there is any structural damage. Complex resection is sometimes possible in malignant lesions where the entire mass has to be excised along with reconstruction of the defect.

B) Resection with Total Cavopulmonary connection – if the malignant lesion involves a large part of the right ventricular musculature and after complete excision insufficient right ventricular musculature remains then both the cavae are directly connected to the pulmonary artery completely bypassing the right ventricle.

C) Resection with Ventricular assist device implantation (VAD) – If a large part of the left ventricular muscle has to be excised, the systemic circulation can be maintained by implantation of either a left ventricular assist device or a total artificial heart (7).

D) Heart Transplantation – In patients where the distant metastasis have been ruled out, Heart Transplantation can be considered. However, in many countries, malignancy is an exclusion criteria for considering a patient for heart transplant.

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiac Tumors (4/4)

Cardiac tumors although an uncommonly encountered entity in the clinical practice, needs attention because a successful management is only possible with timely detection and multidisciplinary treatment.

References

1. McAllister H, Fenoglio J. Tumors of the cardiovascular system. In: Hartmannn W, Cowan W, editors. Atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology; 1978. pp. 1–20.

2. Gunther T, Schreiber C, Noebauer C, Eicken A, Lange R. Treatment strategies for pediatric patients with primary cardiac and pericardial tumors: a 30-year review. Pediatr Cardiol. 2008;29:1071–1076.

3. Klatt EC, Heitz DR: Cardiac metastases. Cancer 65:1456–1459, 1990.

4. Kumar N, Agarwal S, Ahuja A, et al. Spectrum of cardiac tumors excluding myxoma: Experience of a tertiary center with review of the literature. Pathol Res Pract. 2011;207:769–774.

5. Pinede L, Duhaut P, Loire R. Clinical presentation of left atrial cardiac myxoma. A series of 112 consecutive cases. Medicine. 2001;80:159–172.

6. Hoffmeier A, Schmid C, Deiters S, et al. Neoplastic heart disease—the Muenster experience with 108 patients. Thorac Cardiovasc Surg. 2005;53:1–8.

7. Ried M, Rupprecht L, Hirt S, et al. Sequential therapy of primary cardiac lymphoma with cardiectomy, total artificial heart support, and cardiac transplantation.

“DIETARY PATTERNS ARE SET AT A VERY EARLY AGE, SOMEWHERE BETWEEN 4 AND 8 YEARS. THE RESEARCH SHOWS THAT CHILDREN WHO HAVE ESTABLISHED A HEALTHY DIET ARE HEALTHIER IN THELONG RANGE AND LESS LIKELY TO DEVELOP CANCER, HEART DISEASE, STROKE, DIABETES AND OBESITY.”

DR GABRIEL COUSENS

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiotoxicity with anthracyclines in Lymphoma (1/3)

Dr K Govind Babu
Consultant Medical Oncologist, St. Johns Medical College and Hospital, HCG Hospitals, Bangalore
&
Dr S Vishwanath
Consultant Medical Oncologist, Apollo Hospitals, Bengaluru

Non-Hodgkin's lymphoma (NHL) is the most common haematological malignancy and with the standard CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) with rituximab for several histological sub types of NHLs provides high rates of sustained response and cure with good safety profile. [1] Similarly, most patients with Hodgkin lymphoma (HL) are also treated with anthracycline based chemotherapy which results in high rates of cure.

However, cardiac dysfunction, mainly due to anthracyclines, is an important concern with incidence of left ventricular ejection fraction (LVEF) dysfunction seen in close to 60 % of patients. [2-4] Certain important factors which have to be considered include- age of the patient, performance status, co-morbidities like hypertension, type diabetes mellitus and concomitant cardiac issues. Early intervention and close collaboration of oncologist and cardiologist can prevent chemotherapy related cardiotoxicity in patients with lymphoma.

Cardiotoxicity is defined as LVEF decrease with more than 10 percentage points, to a below 50%, evaluated 2–3 weeks after initiation therapy.

A dose of doxorubicin that exceeds 500 mg/ m2 is an important factor in cardiotoxicity, while doses below 300 mg/m2 are considered as low risk.

In a recent retrospective study from Japan, the formation of fragmented QRS was shown to be a surrogate marker of left ventricular dysfunction and heart failure in patients with non-hodgkins lymphoma (NHL) receiving R-CHOP chemotherapy. [5]

Cardiac assessment, including echocardiography is a must for all asymptomatic patients within 6–12 months of completing an anthracycline-containing regimen, as most episodes of cardiotoxicity occur during this early post chemotherapy period. [6]

Various methods have been adopted to mitigate cardiotoxicity of antrhacylines that include, cardio protectants such as amifostine, dexrazoxane or altered schedules of infusions. The role of amifostine as a cardio protectant has declined over time and is no more used in this role. The use of dexrazoxane

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate, Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Cardiotoxicity with anthracyclines in Lymphoma (2/3)

remains but is hampered by its cost and vagaries of its availability. Studies looking at anthracyclines being given as prolonged infusions have shown to decrease cardiotoxicity. Antracyclines were administered as 2, 6 ,12 and 24 hour infusions to study this and the 6 hour infusion seems to be the most time and cost-effective way of administartion.

We have been using this method for three decades now and have hardly encountered any cardiotoxicity.

Long-term cardiac surveillance with echocardiography monitoring as done in specialised cardio-oncology centres can go a long way in detecting this entity. [7]

A recent study by Mihalcea et al showed that early incorporation of certain parameters like 3D **echocardiography assessed LVEF and myocardial deformation: longitudinal (LS), radial, circumferential and area strain can detect early chemotherapy-induced cardiotoxicity and predict LVEF decline. [8]**

Georgakopoulos et al in a study of 147 patients showed that the addition of metoprolol or enalapril didn't provide additional benefit in preventing cardiotoxicity due to anthracyclines in lymphoma. [9]

However, the OVERCOME trial (prevention of left Ventricular dysfunction with Enalapril and Carvedilol in patients submitted to intensive Chemotherapy for the treatment of malignant Hemopathies) showed that enalapril and carvedilol could help in preventing LVEF dysfunction and heart failure. [10]

IL-1RT1 may emerge as a reliable biomarker for unfolding cardiovascular disease (CVD) in diffuse large B cell lymphoma (DLBCL) patients receiving doxorubicin based on a recent study by Morth et al. [11]

To conclude- anthracyclines are important drugs for patients with lymphoma and early detection of cardiotoxicity with novel biomarkers and 3D echocardiography with prompt intervention using drugs like ACEi and beta blockers can reduce risk of long-term cardiac dysfunction and improve quality of life. Simple alteration of infusion time can be very effective. Similarly early post chemotherapy surveillance and long-term monitoring of these patients is important as well.

References:

1. Vidal, L. et al. CHOP-like-14 compared to CHOP-like-21 for patients with aggressive lymphoma: a meta-analysis of randomized controlled trials. Acta Oncol. 55, 77–84 (2016).

2. Zamorano, J. L. et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 37, 2768–2801 (2016).

3. Mihalcea, D. J., Florescu, M. & Vinereanu, D. Mechanisms and genetic susceptibility of chemotherapy-induced cardiotoxicity in patients with breast cancer. Am. J. Ter. 24, e3-11 (2017).

Cardiotoxicity with anthracyclines in Lymphoma (3/3)

4. Plana, J. et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur. Heart J. 27, 911–939 (2014).

5. Gurdogan M, Ozkan U. A Novel Predictor of Chemotherapeutic Cardiotoxicity in Patients with Non-Hodgkin Lymphoma. Oncol Res Treat. 2019;42(7-8):375-381.

6. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, Civelli M, Lamantia G, Colombo N, Curigliano G, Fiorentini C, Cipolla CM. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015 Jun 2;131(22):1981-8.

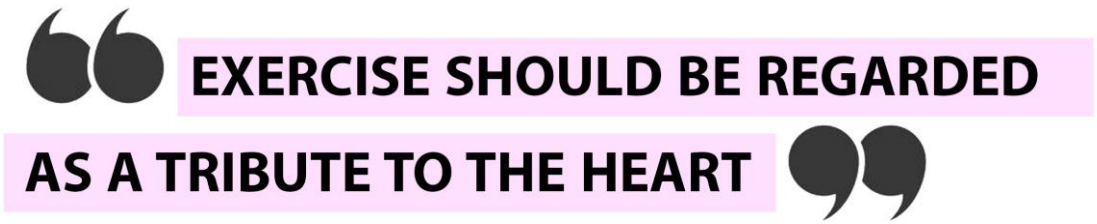
7. Galderisi M, Lyon AR, Van der Meer P, Cohen Solal A, Zamorano JL, Jerusalem G, Moonen M, Aboyans V, Bax JJ, Asteggiano R. Cardio-Oncology Services: rationale, organization, and implementation. Eur Heart J. 2019 Jun 7;40(22):1756-1763.

8. Mihalcea, D., Florescu, M., Bruja, R. et al. 3D echocardiography, arterial stiffness, and biomarkers in early diagnosis and prediction of CHOP-induced cardiotoxicity in non-Hodgkin's lymphoma. Sci Rep 10, 18473 (2020).

9. Georgakopoulos P, Kyriakidis M, Perpinia A, Karavidas A, Zimeras S, Mamalis N, Kouvela M, Charpidou A. The Role of Metoprolol and Enalapril in the Prevention of Doxorubicin-induced Cardiotoxicity in Lymphoma Patients. Anticancer Res. 2019 Oct;39(10):5703-5707.

10. Bosch X, Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, de Caralt TM, Morales-Ruiz M, Perea RJ, Monzó M, Esteve J. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and Carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant Hemopathies). J Am Coll Cardiol. 2013 Jun 11;61(23):2355-62.

11. Mörth, C., Sabaa, A.A., Freyhult, E. et al. Plasma proteome profiling of cardiotoxicity in patients with diffuse large B-cell lymphoma. Cardio-Oncology 7, 6 (2021).



ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

Is Domperidone a Cardiac safe drug? (1/2)

Dr Indu Bansal Aggarwal
Director & Senior Consultant,
Radiation Oncology
Narayana Superspeciality Hospital, Gurugram

Domperidone is a very commonly used drug in oncology practice. It is a peripheral dopamine (D2) receptor antagonist. It exerts its gastro-prokinetic action by blocking GI D2-receptors and as an antiemetic by blocking D2-receptors at the chemo-receptor trigger zone. It is used to treat dyspeptic symptoms that may be associated with delayed gastric emptying and acute symptoms of nausea and vomiting. Unlike other prokinetic agents, it is not associated with central nervous system side effects as it does not cross blood brain barrier.

Although it's a very commonly prescribed over the counter drug in Oncology practice, it has its own share of side effects. The patients may complain of milky discharge from the nipple, gynecomastia, dry mouth, headache, hot flashes, skin irritation, eye irritation or menstrual irregularities. The patients may also complain of change in appetite, constipation, diarrhoea, heartburn, stomach cramps, burning in urination, dizziness, drowsiness, irritable behaviour, decreased strength, crampy legs, nervousness or palpitations. Domperidone overdose may lead to difficulty in speaking, disorientation, dizziness, fainting, irregular heartbeat, light-headedness, loss of balance or muscle control. Rarely fast, irregular, pounding, or racing heartbeat or pulse or swelling of face, hands, lower legs, or feet may happen. The risks are dose dependent and are more with > 30 mg daily for prolonged periods or with Intravenous use and in elderly.

There is some controversy regarding its cardiac side effects as some literature shows risk of QT prolongation and ventricular arrhythmias. The cause is thought to be blockade of hERG voltage-gated potassium channels. We should be careful in prescribing it to patients with pre-existing prolongation of cardiac conduction intervals, significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure. Other risk factors as family history of coronary artery disease, high blood pressure, high blood cholesterol, obesity, diabetes, smoking and excessive alcohol consumption should also be kept in mind.
It's important to keep in mind USA investigational new drug (IND) protocol recommendations for prescribing domperidone: -

(1) Do a baseline and on-treatment ECGs in all patients to see for prolonged QT interval (QTc > 450 ms in males and >470 ms in females);
(2) Do not prescribe it with other medications which prolong the QT interval as well as with cytochrome P450 inhibitors such as clarithromycin, diltiazem, erythromycin, itraconazole, verapamil and ritonavir.
(3) Monitor for electrolyte abnormalities (e.g., hypokalemia and hypomagnesaemia)
(4) Have a high clinical awareness for possible cardiac-related symptoms and outcomes in patients using it for chronic periods.

Is Domperidone a Cardiac safe drug? (2/2)

The dose of domperidone should be the lowest effective dose for the individual situation for the shortest possible duration. The maximum treatment period should not usually exceed one week. For adults and adolescents over 12 years of age and weighing 35kg or more, the recommended maximum dose in 24 hours is 30mg (dose interval: 10mg up to three times a day). For children weighing ≥ 35kg, the dose is 0.25 mg/kg three or four times a day, up to a maximum daily dose of 1.0 mg/kg. In children under 12 years of age and weighing less than 35kg, the recommended maximum dose in 24 hours is 0.75mg/kg body weight (dose interval: 0.25mg/kg body weight up to three times a day). The use in children under 2 years of age is contraindicated.

This drug is not approved in many countries and has to be used with caution in cancer patients.

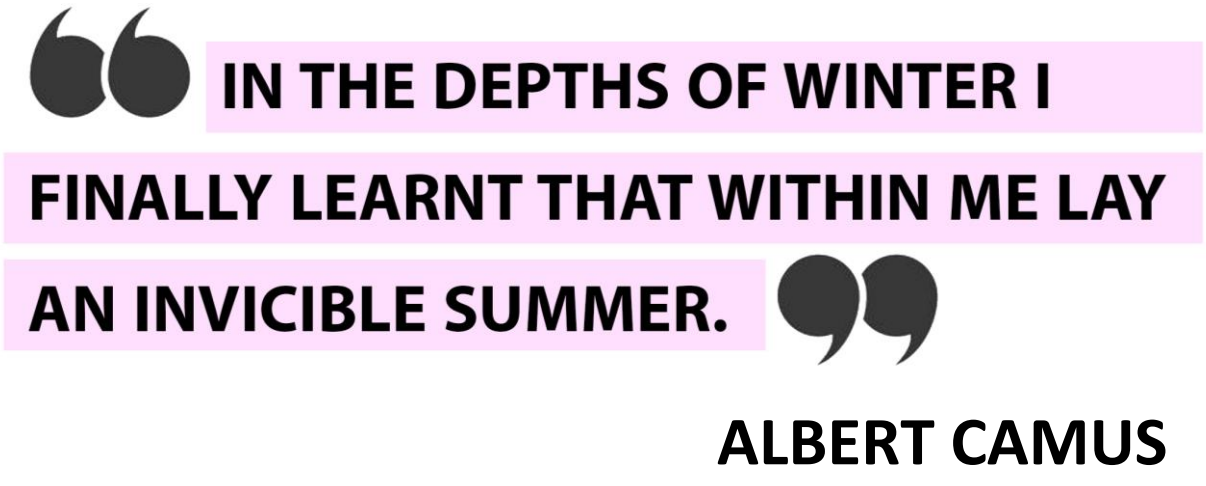
References

1. Song BG, Lee YC, Min Y W, Kim K, Lee H, Son HJ, Rhee PL et al. Risk of domperidone induced severe ventricular arrhythmia. Scientific Reports 2020;10.

2.Bashashati M, Sarosiek I, Siddiqui T, McCallum R et al. Adverse Effects of Domperidone: Prolonged QuesT for Knowledge? Digestive Diseases and Sciences 2016, 61, p3384–86.

3. Hall W. Improving the safety of prescriptions of domperidone in primary care: implementing MHRA advice. BMJ Quality Improvement Reports 2016; u209711.w4039.

4. Cowan A, MD, Garg A, McArthur E, Tsobo F M, Weir M. Cardiovascular Safety of Metoclopramide Compared to Domperidone: A Population-Based Cohort Study. J Canad Assoc Gastroenterology 2021, 4(5) 110–e119.



ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

ACOS Office Bearers (from January 2021)

Patron
Devi Shetty

President
Purvish Parikh

Vice President
Hisham Ahamed

Chairperson Scientific Committee
Sheela Sawant

Honorary Secretary
Vivek Agarwala

Executive Committee
Arman Reza
Ajay Bapna
Hollis Dsouza
Jun Hua Chong
Rakesh Gopal
Randeep Singh
Taro Shiga
Venugopal Krishnan Nair

Chairperson Newsletter Committee
Indu Bansal Aggarwal

Supporting Societies/ Organizations

IASCO
SFO
ICON Trust
SAJC
IJMIO

Scientific Committee
Prafulla Kerkar
Nishit Chandra
Hemant Madan
Amit Agarwal
Vikas Talreja
MV Chandrakanth
Purna Kurure
Deepak Padmanabhan
Vamshi Krishna Muddu

Newsletter Committee
Indu Bansal Aggarwal
Anuprita Daddi
Bhavesh Parekh
Elizabeth Joseph
Govind Babu

Country Representative
Bangladesh - Syed Mohd Akram Hossain
Japan - Taro Shiga
Nepal - Sheelendra Shakya
Oman - Ajit Venniyoor
Pakistan - Zeba Aziz
Singapore - Jun Hua Chong
Sri Lanka - Iqbal Ahamed
UK - Arjun Ghosh
USA - Avirup Guha

Representatives of Supporting Organizations
Amit Bhatt
Amit Joshi
Ghanashyam Biswas

ACOS Newsletter
www.acos.info
AsianCardioOncologySociety@gmail.com
Editor: Dr Indu Bansal Aggarwal
Vol 1
Issue 4
Jan - March
2022

ACOS Membership Form

First Name_____Middle Initials_____

Last Name_____

City _____ WhatsApp _____

PIN_____ Mobile: _____

E mail: _____ @ _____

PAN Card No ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Main Hospital Affiliation: _____

Main Designation: _____

1. Membership will be as per eligibility criteria and rules of Asian Cardio-Oncology Society.
2. Membership fees are Rs 2,500/- for the year 2022.
3. Submission of completed application form using google link is mandatory.

Payment to be made via net banking to:

Account Name	: K C LLP A/c ACOS
Account Number	: 5921-004-478-9221
Bank Name	: HDFC Bank
Bank Branch	: Prabhadevi Branch, 385 Veer Savarkar Road, Prabhadevi, Mumbai 400025
Bank IFSC Code	: HDFC0000012

Signature_____

Date: _____ Place_____

Membership request details MUST be filled online at
https://forms.gle/umnXJGiqUSjamoAq6

ACOS Secretariat: Kavina Creations, Unit 3, Ground Floor, Unique Industrial Estate,
Twin Tower Lane, Prabhadevi, Dadar West, Mumbai 400025
Tele: +91 98210 25850 *Email: info@kavinacreations.com