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EXPERT PANEL

Cardio-Oncology Recommendations for Pediatric Oncology Patients

An Australian and New Zealand Delphi Consensus

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ABSTRACT

Cardio-oncology is a new multidisciplinary area of expertise that seeks to pre-emptively and proactively address cardiac complications that emerge during and following cancer therapy. Modern therapies including molecular targeted therapy and immunotherapy have broadened the agents that can cause cardiac sequelae, often with complications arising within days to weeks of therapy. Several international guidelines have been developed for the acute monitoring of cardio-oncology side effects. However, none are specific to pediatrics. We have addressed this gap in the literature by undertaking a rigorous Delphi consensus approach across 11 domains of cardio-oncology care using an Australian and New Zealand expert group. The expert group consisted of pediatric and adult cardiologists and pediatric oncologists. This Delphi consensus provides an approach to perform risk and baseline assessment, screening, and follow-up, specific to the cancer therapeutic. This review is a useful tool for clinicians involved in the cardio-oncology care of pediatric oncology patients. (JACC Adv 2022;1:100155) Crown Copyright © 2022 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

CCS = childhood cancer survivors

CTRCD = cancer therapeutic-related cardiac dysfunction

LV = left ventricle

LVEF = left ventricle ejection fraction

MS = metabolic syndrome

VEGF = vascular endothelial growth factor

Recent advances in pediatric oncology have resulted in survival rates of >80%.[1] However, improving long-term chronic and serious health outcomes in survivors remains an important and essential focus. Cardiac complications of therapy are a leading cause of morbidity and mortality in pediatric cancer survivors, second only to disease relapse.[2] The multidisciplinary area of cardio-oncology has emerged to pre-emptively and proactively address cardiac complications arising from cancer therapies including radiotherapy, chemotherapy, targeted therapies, and immunotherapy.[3-14]

Cardiac complications from cancer therapy are specifically linked to the therapy used. Anthracycline chemotherapies were first described in 1967 and have been the most-studied cardiotoxic chemotherapy.[15] Anthracycline use can cause a hypokinetic progressive cardiomyopathy resulting in end-stage cardiac failure.[16] Lifetime cumulative dose exposure has been cited as the strongest risk factor for anthracycline cardiomyopathy. Long-term pediatric data indicate there is no significantly increased risk for anthracycline doses below 100 mg/m^2.[17] Treatment and screening for late-onset heart failure is beyond the scope of these guidelines. Newer therapies have been linked to a range of cardiovascular sequelae, some of which occur immediately or soon after commencing therapy[18] (**Table 1**). The use of novel therapeutics has broadened the focus on timing of cardiac toxicity from late effects to both acute and late toxicities, warranting closer surveillance and earlier monitoring.

Several adult international guidelines and position statements have been developed for the acute and long-term[4,19-24] monitoring of cardio-oncology side effects. No pediatric oncology guidelines exist for the surveillance or screening of acute cardiovascular toxicities from molecular therapies or immunotherapies.

This study uses a Delphi consensus approach which has been proven to be a reliable measurement instrument in developing new concepts and setting the direction of future-orientated research. The technique seeks to reach consensus through repeated rounds of questioning, with refinement of questions based on consensus with each round. Using this approach, we sought to: 1) define a high-risk population to be seen within cardio-oncology clinics during an acute therapy; 2) define during-therapy recommendations; and 3) provide recommendations specific to cancer therapies including new molecular therapies and immunotherapies.

HIGHLIGHTS

- Prior to this Delphi expert consensus approach to cardio-oncology, guidelines did not exist for pediatric patients during therapy. Cardio-oncology guidelines exist for the acute management of cardiovascular toxicities from traditional and more modern therapies in adult cancer patients.
- This study provides guideline recommendations for which high-risk patients should be reviewed in cardio-oncology clinics.
- Addresses the minimum baseline investigations for patients according to the cancer therapeutic being received.
- Provides guidance for frequency of follow-up for patients receiving chemotherapy, radiotherapy, and molecular inhibitors.

METHODS

A Delphi approach was used to reach consensus for appropriate cardio-oncology risk stratification, surveillance, and management, according to therapy type in pediatric oncology patients during an acute therapy (**Central Illustration**). Acute therapy was defined as patients currently receiving a therapy. This study was approved by The Royal Children's Hospital Human Research Ethics Committee (HREC 78222).

STUDY PARTICIPANTS. Participants were identified as experts in pediatric cardiology, oncology, or radiology fields, through the Australian Cardio Oncology Registry and Biobank steering committee.[25] In addition, the Australian New Zealand Children's Haematology Oncology Group assisted in identification of clinical experts. A minimum of 25 experts combined from pediatric cardiology, oncology, and radiology were necessary to use the Delphi approach. Once the experts were identified, the participants were sent a letter of implied consent with individual links to the online Welphi platform.[26]

DEFINING THE DELPHI DOMAINS. Pediatric cardio-oncology domains for acute surveillance were created using the current published European and American Adult cardio-oncology guidelines[19-23,27] and adapted for pediatric oncology patients by the study principal investigator. Elements of pediatric late-effect

TABLE 1 Cardiac Complications Associated With Molecular, Targeted Therapies and Immune Checkpoint Inhibitors

Drug Class	Proteasomal Inhibitors	HER2 Inhibitors	VEGF Inhibitors	BCR-Abl Inhibitors	BTK Inhibitors (Ibrutinib)	Immune Checkpoint Inhibitors	Anthracyclines	mTOR Inhibitors
QTc prolongation			■	■	■			
Left ventricular dysfunction	■	■	■		■		■	
Left ventricular failure	■	■	■	■	■		■	
Hypertension	■		■	■	■			
Myocardial ischemia	■		■					
Arterial thrombotic events			■	■				
Conduction disorders			■	■	■	■		
Accelerated atherosclerosis				■				
Acute coronary syndrome				■		■		
Stroke				■				
Hyperglycemia				■				■
Hypercholesterolemia				■				■
Atrial fibrillation					■			
Myocarditis						■		
Pericarditis						■	■	
Pulmonary arterial hypertension					■			
Takotsubo syndrome							■	

Cardiac complications listed include those related to proteasomal inhibitors,[6] HER2 inhibitors,[7] VEGF inhibitors,[8] BCR-Abl inhibitors,[9,10] BTK inhibitors,[11] immune checkpoint inhibitors,[12] anthracyclines,[13] and mTOR inhibitors.[14]

BTK = Bruton tyrosine kinase; mTOR = mechanistic target of rapamycin; VEGF = vascular endothelial growth factor.

guidelines were also incorporated.[24,28] This generated 54 questions across 11 domains; the approach to defining the domains and consensus is summarized in **Figure 1** and the Supplemental Appendix.

DEFINING CARDIO-ONCOLOGY GUIDELINES. Question selection and creation were designed with the intention of driving consensus for cardio-oncology surveillance for pediatric oncology patients in the acute phase of care. The initial questions were designed by the academic leads of the study (academic pharmacist, 2 pediatric oncologists, 2 pediatric cardiologists, and 2 adult cardiologists). Published adult recommendations, related to each domain, formed the basis of each question. Questions were formatted as: 1) qualitative (fixed Likert scale "strongly agree," "agree," "neutral," "disagree," "strongly disagree"); 2) ranking; or 3) survey (open- and closed-ended questions).

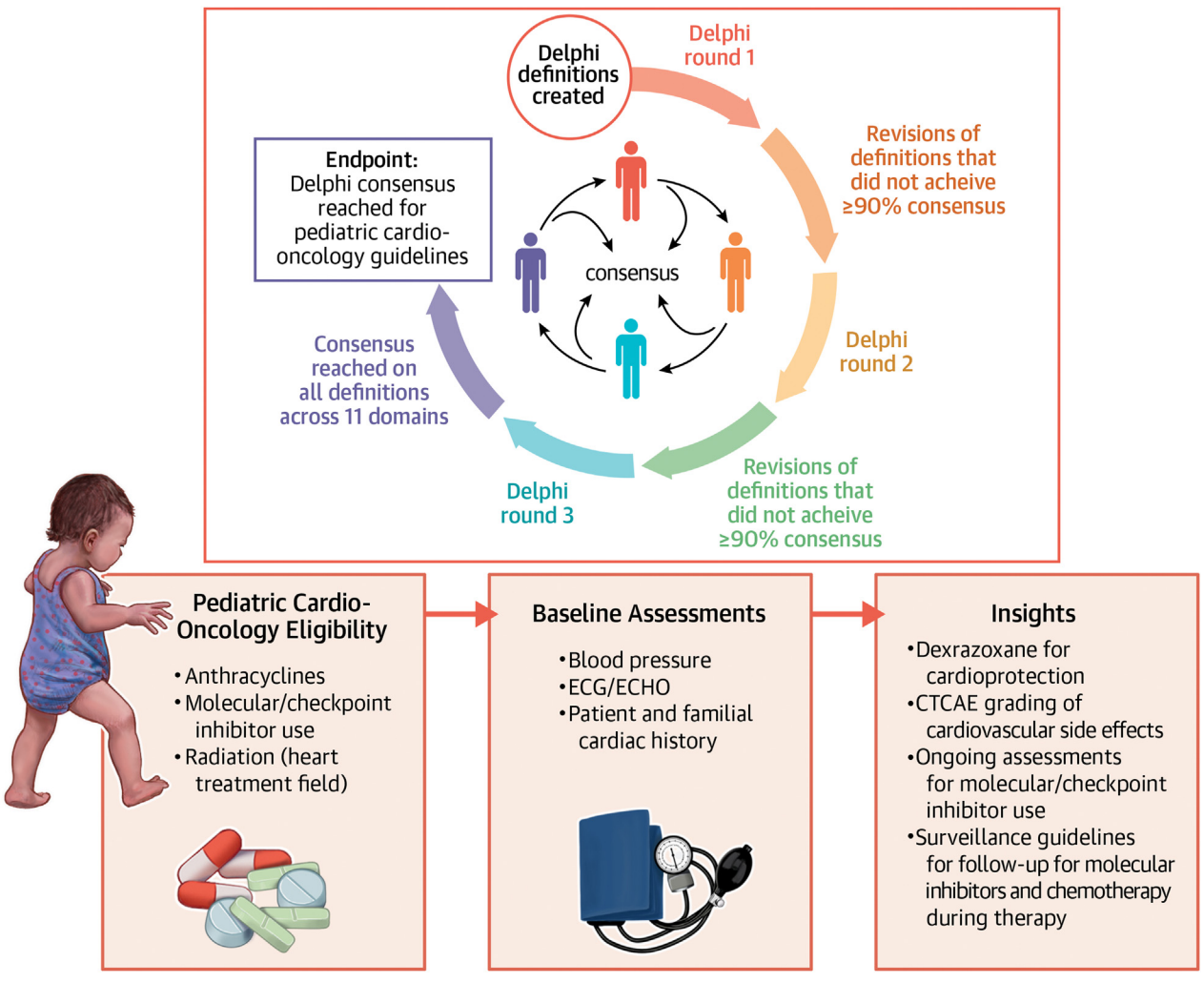
DEVELOPING EXPERT CONSENSUS OPINION. Once questions for each domain were defined, they were evaluated using a modified Delphi process (Supplemental Appendix). Researchers used the online questionnaire platform Welphi to implement the Delphi method and to run the questionnaires. The Welphi platform facilitates this process and allows for the anonymous participation of participants. It was chosen to enhance expert participation among a group who are geographically dispersed and have competing clinical demands. In addition, as the participants complete the questionnaire individually, potential bias via the "groupthink" phenomena is removed. Consensus for each domain was defined as ≥90% of agreement. Agreement was defined as a response of "agree" or "strongly agree" on the Likert scale. There was no minimum number of rounds required for consensus.

After each round, participants' responses were aggregated within the platform before being exported and analyzed by a focus group of experts. When questions did not achieve a consensus of ≥90%, these questions were then revised by the focus group, taking into account the current literature and anonymous comments of participants before resubmission in the subsequent round. Preliminary consensus and nonconsensus outcomes, together with comments and newly defined questions for each domain, were circulated to all participants.

RESULTS

Consensus definitions of the cardio-oncology guidelines for each of the 11 domains are shown in **Tables 2 to 5**, with a summary of the overall guideline in **Figure 2**. A total of 35 experts were approached, of which 29 responded. In round 1, there were 17 pediatric oncologists (58%) and 12 pediatric cardiologists (42%) (Supplemental Appendix). These experts

CENTRAL ILLUSTRATION This Research Sought to Provide a Framework for Pediatric Oncology Patients Seen During Active Therapy



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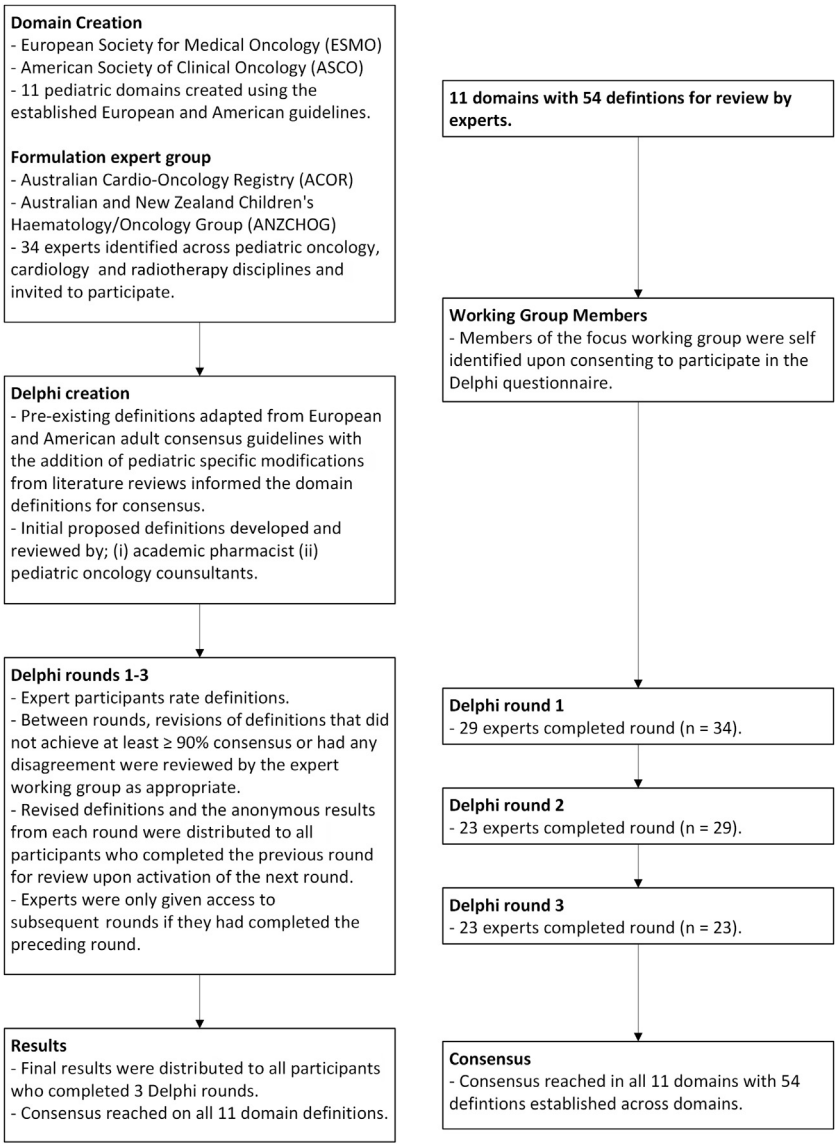
CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram.

met diversity requirements with backgrounds in pediatric cardiology, oncology, or radiology fields with representation from most national pediatric institutes. Gender diversity was also observed, with 51% female and 49% male participants represented among the experts. Participation was 29/34 (85%) in round 1, 23/29 (79%) in round 2, and 23/23 (100%) in round 3.

DOMAIN 1: DEFINING HIGH-RISK PEDIATRIC ONCOLOGY PATIENTS WHO SHOULD BE REVIEWED BY EXPERTS IN CARDIO-ONCOLOGY DURING ACUTE THERAPY. For this domain, we defined "reviewed" as an in-person or telehealth clinic review of the patient with their parent/guardian. Cardio-oncology here is defined as a clinic consisting of a multidisciplinary team of cardio-oncology specialists. The cardio-oncology multidisciplinary at a minimum should consist of cardiologists and oncologists who have expertise in cardio-oncology through either: 1) academic; and/or 2) clinical care. For those centers that do not have a cardio-oncology clinic, patients can be seen by cardiologists and oncologists with expertise in cardio-oncology, outside of an multidisciplinary clinic.

The experts agreed that a high-risk patient was one who was receiving high-dose radiotherapy to 35 Gy and any patient who received any dose of anthracycline together in combination with at least 15 Gy of

FIGURE 1 Process Leading to Consensus Definitions, Surveillance, and Management Approaches Within Pediatric Cardio-Oncology



radiation where the heart was within the radiotherapy field. High risk was assigned to all patients who had or will receive ≥250 mg/m^2 of a doxorubicin equivalent. Furthermore, patients receiving vascular endothelial growth factor (VEGF) inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, proteasomal inhibitors, or immune checkpoint inhibitors should be reviewed at least once within a cardio-oncology clinic, with the recognition that the necessity for reviewing more than once may arise as new evidence emerges in the discipline. Consensus was also reached for high-risk patients who should be reviewed within a cardio-oncology clinic: in circumstances where clinicians screen for metabolic syndrome (MS) in pediatric cancer patients and an MS diagnosis is made; patients with chronic kidney disease; and adolescent and young adult patients who are pregnant at the time of receiving any cancer therapy.

DOMAIN 2: DEFINING A MINIMUM SET OF STANDARD INVESTIGATIONS FOR CARDIO-ONCOLOGY PATIENTS WHO ARE AT HIGH RISK OF CARDIOTOXICITY DURING ACUTE THERAPY. The minimum level of investigation includes a cardiac and family history and the exploration of modifiable lifestyle factors. The imaging modality preferred by consensus was 3-dimensional transthoracic echocardiogram as it was thought to offer advantages particularly with respect to

TABLE 2 Consensus Definitions for Pediatric Cardio-oncology (Domains 1-2): The High-Risk Patient and Standard Investigations

Domains	Consensus Definitions/Approach
Domain 1	*Defining high-risk pediatric oncology patients that should be reviewed by experts in cardio-oncology during acute therapy.* A patient will be considered to be at high risk if: • They have received a total cumulative dose ≥250 mg/m^2 (doxorubicin equivalent). • The patient has relapsed and the cumulative doxorubicin equivalent dose (as part of first- or second-line therapy) will be ≥250 mg/m^2. • They have received any dose of anthracycline combined with radiotherapy ≥15 Gy and where any area of the heart is involved in the treatment field as part of first- or second-line therapy. • They have received radiotherapy ≥35 Gy and where any area of the heart is involved in the treatment field as part of first- or second-line therapy. • They have pre-existing congenital heart disease, a relevant family history of cardiovascular disease (including genetic disorders that impact heart structure and storage disorders but excluding adult-type cardiac disease, ie, myocardial ischemia, coronary artery disease, etc) and those with previous abnormal left ventricular dysfunction. • They are receiving treatment with VEGF inhibitors, mTOR inhibitors, proteasomal inhibitors, checkpoint inhibitors. They should ideally be seen at least once within a cardio-oncology clinic (if facilities exist), or more frequently to manage any potential associated cardiotoxicities as evidence emerges. • In circumstances where the clinician screens for metabolic syndrome in pediatric cancer patients and are diagnosed with metabolic syndrome.[a] • They have chronic kidney disease. • They are an adolescent or young adult patient who is pregnant while receiving cancer therapy.
Domain 2	*Defining a minimum set of standard investigations for cardio-oncology patients that are at high risk of cardiotoxicity during acute therapy* At the initial cardio-oncology clinic patient consultation: • Baseline measurements should include point-of-care blood pressure and ECG along with an assessment for the risk of metabolic syndrome. • A cardiovascular global risk assessment should be conducted (as per institutional guidelines) or an agreed upon cardiovascular health risk assessment tool. • Cardiovascular assessment should at a minimum include a cardiac and family history and, where age appropriate, lifestyle factors. • The same imaging modality should be used for surveillance throughout treatment unless a change in image modality is driven by a change in the overall patient clinical need. • 3-dimensional TTE measurements of left ventricular ejection function with global longitudinal strain is the optimal recommendation for surveillance. In the absence of 3-dimensional TTE, 2-dimensional TTE measurements of left ventricular ejection function with global longitudinal strain would be appropriate. • Echocardiogram assessment should include measurements of ejection fraction, fractional shortening, left ventricular wall stress, decreased left ventricular mass, velocity of shortening corrected for heart rate, left ventricular thickness to dimension ratio, and diastolic dysfunction as a minimum. • A cardiac MRI should be conducted (if facilities exist) if the quality of the repeated TTE is suboptimal Towards the completion of therapy: • Patient education and information should be provided to manage any modifiable cardiovascular risk factors (ie, obesity education and awareness, optimization of physical activity, healthy eating).

[a]In making a metabolic syndrome diagnosis: Obesity is defined as a BMI >95th percentile and the diagnosis of hypertension, diabetes, or dyslipidemia has been made by a physician or the patient is taking medication for these conditions.

BMI = body mass index; ECG = electrocardiogram; MRI = magnetic resonance imaging; mTOR = mechanistic target of rapamycin; TTE = transthoracic echocardiogram; VEGF = vascular endothelial growth factor.

TABLE 3 Consensus Definitions for Pediatric Cardio-Oncology (Domain 3); Surveillance and Toxicity Management for Patients Receiving Anthracycline Therapy

Domain	Consensus Definitions/Approach
Domain 3	*Defining surveillance and toxicity management for patients receiving anthracycline therapy* • For patients receiving anthracyclines: • If a patient is receiving a cumulative anthracycline dose ≥250 mg/m^2 (doxorubicin equivalent), it is recommended the patient has a cardio-oncology review (if facilities exist) at the beginning of the first treatment cycle as optimal therapy or as soon as is practical so that therapy is not delayed. • Patients should be considered to be at high risk and receive dexrazoxane if: • The patient is younger than 5 y at diagnosis and is receiving any dose of anthracycline plus any dose of radiation where any area of the heart is in the treatment field. • If the patient is receiving ≥100 mg/m^2 of cumulative anthracycline dose (doxorubicin equivalent) and is also receiving radiotherapy ≥15 Gy where any area of the heart is in the treatment field. • If the patient has advanced disease and/or has received a total cumulative anthracycline dose ≥250 mg/m^2 (doxorubicin equivalent). • Patients who have an LVEF <40% regardless of symptoms should receive ACE inhibitors and/or beta-blockers. • The pre-emptive use of heart failure medication (ie, ACE inhibitors, beta-blockers) for patients with an LVEF <50%, regardless of symptoms, should form part of prospective cardio-oncology trials to guide treating clinicians. • Additional biomarkers (ie, troponin I) as screening for cardiotoxicity in the acute phases of therapy are still exploratory in pediatric oncology. Any screening with biomarkers should form part of pediatric pilot cardio-oncology trials.

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction.

TABLE 4 Consensus Definitions for Pediatric Cardio-Oncology (Domains 4-9); Surveillance and Toxicity Management for Patients Receiving VEGF Inhibitors, mTOR Inhibitors, BCR-Abl Kinase Inhibitors, Proteasomal Inhibitors, BTK Inhibitors, and Checkpoint Inhibitors

Domains	Consensus Definitions/Approach
Domain 4	*Defining cardio-oncology surveillance and toxicity management for patients receiving VEGF inhibitors.* • Assessment prior to commencing VEGF inhibitors should include a point-of-care blood pressure measurement, a calculation of renal function and measurement of proteinuria. • A follow-up appointment within the first month of therapy is warranted by the cardiologist or oncologist (given hypertension occurs within a 1- to 2-wk period) • A review of toxicities associated with VEGF inhibitors (whether this is by cardiologist or oncologist) should be performed at a minimum of every 3 mo (or earlier if protocol mandates). • If after 12 mo of therapy the patient has not required any VEGF inhibitor dose modifications due to toxicities, a review can be performed every 6 mo (or earlier if protocol mandates). • Any patient who has ongoing documented toxicities should be considered for discussion at a cardio-oncology multidisciplinary team meeting.
Domain 5	*Defining cardio-oncology surveillance and toxicity management for patients receiving mTOR inhibitors.* • Assessment prior to commencing mTOR inhibitors should include a point of care blood pressure measurement, blood glucose levels, lipid profile and renal function. • Surveillance and evaluation of baseline indices (blood pressure, blood glucose levels, lipid profile and renal function) should be conducted on at least a 6 monthly basis. • If after 12 mo of therapy the patient has not required any mTOR inhibitor dose modifications due to toxicities, a review can be performed every 12 mo (or earlier if protocol mandates). • Any patient who has ongoing documented toxicities should be considered for discussion at a cardio-oncology multidisciplinary team meeting.
Domain 6	*Defining cardio-oncology surveillance and toxicity management for patients receiving BCR-Abl kinase inhibitors.* • Cardio-oncology evaluation should be conducted prior to commencement (if facilities exist) and include an ECG and echocardiogram along with an examination by an oncologist. • Patients receiving BCR-Abl kinase inhibitors should have an ECG and cardiovascular risk assessment completed before initiation of imatinib and dasatinib in a cardio-oncology clinic. • Patients should have a cardiovascular risk assessment completed before initiation of ponatinib and nilotinib by an oncologist. • Ponatinib and nilotinib are reported as inducing both hypertension and thromboembolic events. Although there is limited evidence yet in pediatric patients, patients should have a cardiovascular risk assessment completed before the initiation of therapy by an oncologist and (where facilities exist) in a cardio-oncology clinic. • Any investigation of peripheral artery disease screening for patients on ponatinib or nilotinib by ankle brachial index measurement and Doppler ultrasound of supra-aortic/lower extremities arteries should be performed in the context of a pilot cardio-oncology trial. • A review of toxicities associated with BCR-Abl kinase inhibitors by either an oncologist or cardiologist should be performed at a minimum of every 3 mo (or earlier if protocol mandates). • If after 12 months of therapy, the patient has not required any BCR-Abl kinase inhibitor dose modifications due to toxicities, a review can be performed every 6 mo (or earlier if protocol mandates). • Any patient who has ongoing documented toxicities should be considered for discussion at a cardio-oncology multidisciplinary team meeting.
Domain 7	*Defining cardio-oncology surveillance and toxicity management for patients receiving proteasomal inhibitors* • As hypertension is the most common cardiac side effect seen with proteasomal inhibitors, point-of-care blood pressure measurements should be performed with each patient review. • A review of toxicities associated with proteasomal inhibitors by either an oncologist or cardiologist should be performed at a minimum of every 3 mo (or earlier if protocol mandates). • If after 12 mo of therapy the patient has not required any proteasomal inhibitor dose modifications due to toxicities, a review can be performed every 6 mo (or earlier if protocol mandates). • Any patient who has ongoing documented toxicities should be considered for discussion at a cardio-oncology multidisciplinary team meeting.
Domain 8	*Defining cardio-oncology surveillance and toxicity management for patients receiving BTK inhibitors (ibrutinib) therapy* • Patients should be screened for arrhythmias during ibrutinib therapy. If at any time point during treatment with ibrutinib the patient develops symptoms concerning for an arrhythmia (ie, palpitations, dizziness, unexplained loss of consciousness), the patient should be referred to a cardiologist. • A review of toxicities associated with ibrutinib therapy by either an oncologist or cardiologist should be performed at a minimum every 3 mo (or earlier if protocol mandates). • If the patient has not required any ibrutinib dose modifications assessment for toxicities after 12 mo of therapy, a review can be performed every 6 mo (or earlier if protocol mandates). • Any patient who has ongoing documented toxicities should be considered for discussion at a cardio-oncology multidisciplinary team meeting.
Domain 9	*Defining cardio-oncology surveillance and toxicity management for patients receiving checkpoint inhibitors* • Cardio-oncology evaluation during immune checkpoint inhibitor therapy should include: • An ECG and troponin I before treatment commences • An ECG and troponin I completed at any time within 48 h prior to the administration of any immune checkpoint inhibitor dose. • An additional echocardiogram and troponin I if the patient develops new cardiovascular symptoms during treatment • Patient admission for diagnostic workup if at any stage myocarditis is suspected.

BTK = Bruton's tyrosine kinase; ECG = electrocardiogram; mTOR = mechanistic target of rapamycin; VEGF = vascular endothelial growth factor.

TABLE 5 Consensus Definitions for Pediatric Cardio-Oncology (Domains 10-11); Surveillance and Management of Prolonged QTc and Immune Checkpoint Inhibitor Myocarditis

Domains	Consensus Definitions/Approach
Domain 10	*Defining cardio-oncology surveillance and management of prolonged QTc.* For patients with a CTCAE grade I or grade II QTc prolongation (v5 or most up to date) and who may be asymptomatic: • Check and correct any electrolyte abnormalities • Where possible cease any unnecessary QTc prolonging agents and; • Repeat an ECG in 48 h. For patients with a CTCAE grade III QTc prolongation (v5 or most up to date) including those who may be asymptomatic: • Check and correct any electrolyte abnormalities • Where possible cease any unnecessary QTc prolonging agents and; • Seek a formal cardiology review. • Cease all cancer therapies in consultation with the patient's treatment protocol and recommence cancer therapy once QTc normalizes (if no evidence of ventricular arrhythmias).
Domain 11	*Defining cardio-oncology toxicity surveillance for immune checkpoint inhibitors.* In the event of *suspected* myocarditis by a clinician, the following steps and/or actions are proposed as appropriate interventions: • Withhold immune checkpoint inhibitor. • Urgent admission to a monitored bed. • Cardio-oncology evaluation with ECG, TTE, CK, CK-MB, and cardiac MRI. • Rule out acute coronary syndrome. • Check for other immune checkpoint inhibitor AEs (myositis, myasthenia gravis, pneumonitis). • Discuss endomyocardial biopsy with cardiology department. In the event of *definite* myocarditis diagnosed by a clinician, the following steps and/or actions are proposed as appropriate interventions: • Withhold immune checkpoint inhibitor. • Urgent admission to a monitored bed. • Cardio-oncology evaluation with ECG, TTE, CK, CK-MB, and cardiac MRI. • Symptomatic treatment of heart failure, arrythmia, and/or conduction abnormality. • Withhold immune checkpoint inhibitor therapy.

AE = adverse event; CK = creatine kinase; CTCAE = common terminology criteria for adverse events; ECG = electrocardiogram; MB = myoglobin binding; MRI = magnetic resonance imaging; TTE = transthoracic echocardiogram.

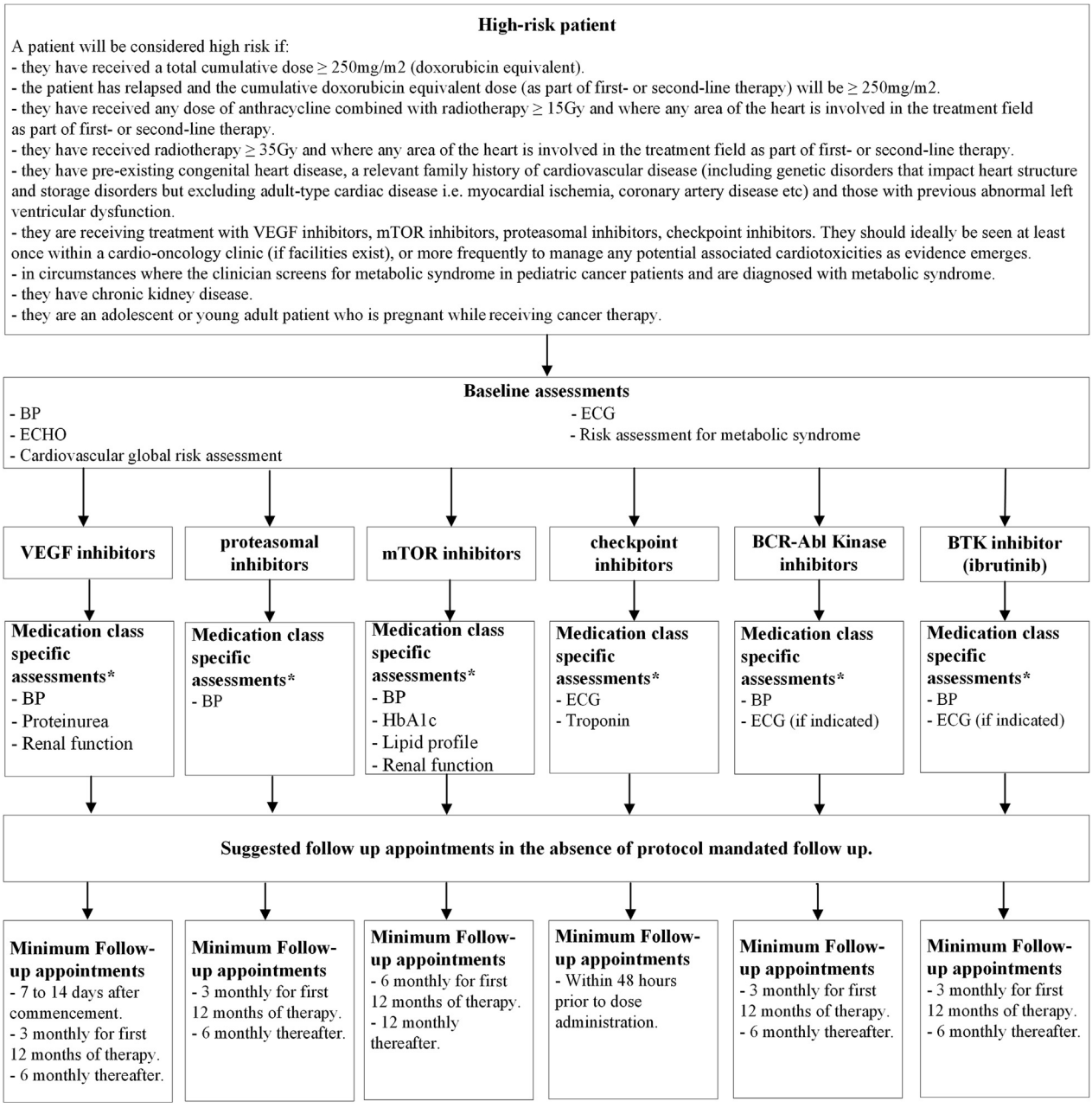
analyzing ventricular volumes and allowing imaging across multiple planes.[29] However, in the absence of cardio-oncology facilities or access to 3-dimensional transthoracic echocardiograms, the use of 2-dimensional transthoracic echocardiograms is recommended. Measurements of left ventricular ejection fraction (LVEF), fractional shortening, left ventricular (LV) wall stress, LV mass, velocity of shortening corrected for heart rate, the ratio of LV thickness to dimension should be conducted as a minimum assessment by either imaging modality. Toward the completion of the therapy, patient education and information should be provided around modifiable cardiovascular risk factors.

DOMAIN 3: DEFINING SURVEILLANCE AND TOXICITY MANAGEMENT FOR PATIENTS RECEIVING ANTHRACYCLINE THERAPY. Where facilities exist, a review in a cardio-oncology clinic prior to the first cycle of therapy was deemed appropriate. Cardio-protection, specifically dexrazoxane, was recommended in high-risk patients (those receiving a cumulative anthracycline dose ≥250 mg/m^2 [doxorubicin equivalent]). Heart failure medications (angiotensin-converting enzyme [ACE] inhibitors and beta-blockers) were recommended in patients with an EF <40%, but not supported pre-emptively in patients with an EF <50% but >40%. Many experts recommended consultation with a cardiologist to decide whether to commence heart failure medications for patients with an EF <50% but >40%. Finally, the use of biomarkers (ie, troponin I) should only be used for cardiotoxicity screening as part of pediatric pilot cardio-oncology trials.

DOMAIN 4: DEFINING CARDIO-ONCOLOGY SURVEILLANCE AND TOXICITY MANAGEMENT FOR PATIENTS RECEIVING VEGF INHIBITORS. VEGF inhibitors include bevacizumab, sorafenib, sunitinib, nilotinib, pazopanib, and dasatinib. Patients should have point-of-care blood pressure measurement, a calculation of renal function, and measurement of proteinuria as a minimum assessment prior to commencing VEGF inhibitors. A follow-up appointment within the first month of therapy was deemed appropriate with either a cardiologist or oncologist to reflect the usual timing of hypertension onset. After 12 months of therapy, if the patient had not required any drug dose modifications due to toxicities, it was agreed that reviews could be conducted 6 monthly (or earlier if protocols mandate).

DOMAIN 5: DEFINING CARDIO-ONCOLOGY SURVEILLANCE AND TOXICITY MANAGEMENT FOR PATIENTS RECEIVING mTOR INHIBITORS. mTOR Inhibitors include temsirolimus and everolimus. Patients receiving mTOR inhibitors should have point-of-care blood pressure, blood glucose, lipid

FIGURE 2 High-Risk Definition, Minimum Screening, and Follow-Up for Novel Inhibitors



*In addition to the baseline assessment, medication class-specific assessments should be conducted at baseline and monitored as appropriate in follow-up appointments. BP = blood pressure; ECG = electrocardiogram; mTOR = mechanistic target of rapamycin; VEGF = vascular endothelial growth factor.

profile, and renal function at baseline. The experts agreed that these parameters should be repeated at 6-monthly intervals.

DOMAIN 6: DEFINING CARDIO-ONCOLOGY SURVEILLANCE AND TOXICITY MANAGEMENT FOR PATIENTS RECEIVING BCR-ABL KINASE INHIBITORS. BCR-Abl kinase inhibitors include imatinib, dasatinib, panotinib, and nilotinib. Patients receiving BCR-Abl kinase inhibitors could be reviewed, where cardio-oncology clinics exist, prior to commencing treatment. In the absence of such a clinic, patients are ordinarily monitored by a treating oncologist. Electrocardiogram and echocardiogram are recommended as part of the initial assessment. For patients receiving ponatinib or nilotinib, a cardiovascular assessment (domain 2) was recommended. Screening for a peripheral artery disease (Doppler ultrasound and ankle brachial index) was not recommended routinely, but as part of a pilot cardio-oncology trials. If the patient had not required any drug dose modifications due to toxicities after 12 months of therapy, it was agreed that reviews could be conducted 6 monthly (or earlier if protocols mandate).

DOMAIN 7: DEFINING CARDIO-ONCOLOGY SURVEILLANCE AND TOXICITY MANAGEMENT FOR PATIENTS RECEIVING PROTEASOMAL INHIBITORS. Proteasomal inhibitors include carfilzomib, bortezomib, and ixazomib. Patients receiving proteasomal inhibitors should have point-of-care blood pressure monitoring routinely. Review of toxicities should occur by either an oncologist or cardiologist, at a minimum of every 3 months (or earlier if protocols mandate). If the patient has not required any dose modifications for toxicities after 12 months of therapy, it was agreed reviews could be performed every 6 months (or earlier if protocol mandates).

DOMAIN 8: DEFINING CARDIO-ONCOLOGY SURVEILLANCE AND TOXICITY MANAGEMENT FOR PATIENTS RECEIVING BRUTON'S TYROSINE KINASE INHIBITORS THERAPY. Bruton's tyrosine kinase (BTK) inhibitors include ibrutinib. A review of toxicities associated with the ibrutinib therapy should be performed by either an oncologist or cardiologist at a minimum of every 3 months. Referral to a cardiologist was recommended if the patient develops symptoms concerning for an arrythmia (ie, palpitations, dizziness, loss of consciousness). If the patient has not required any dose modifications after 12 months of therapy, assessment for toxicities can be performed every 6 months (or earlier if protocol mandates).

DOMAIN 9: DEFINING CARDIO-ONCOLOGY SURVEILLANCE AND TOXICITY MANAGEMENT FOR PATIENTS RECEIVING CHECKPOINT INHIBITORS. Checkpoint inhibitors include pembrolizumab, ipilimumab, nivolumab, and atezolizumab. Patients should be pre-emptively evaluated for myocarditis. An electrocardiogram and biomarkers (ie, troponin I) should be performed and repeated within 48 hours prior to each administered checkpoint inhibitor dose and, additionally, if patients become symptomatic.

DOMAIN 10: DEFINING CARDIO-ONCOLOGY SURVEILLANCE AND MANAGEMENT OF PROLONGED QTc. Patients with a Common Terminology Criteria for Adverse Events (CTCAE) grade I or II QTc prolongation (regardless of symptoms) should have any electrolyte abnormalities corrected, cessation of unnecessary QTc prolonging agents, and a repeat electrocardiogram in 48 hours. Patients with a CTCAE grade III or IV QTc prolongation (regardless of symptoms) should have any electrolyte abnormalities corrected, cease the use of unnecessary QTc prolonging agents, and be referred to cardiology. In addition, all cancer therapies should only be discontinued in consultation with the patient's protocol and not recommenced until the QTc normalizes. A list of medications that can cause QTc prolongation are listed in the Supplementary.

DOMAIN 11: DEFINING CARDIO-ONCOLOGY TOXICITY SURVEILLANCE FOR IMMUNE CHECKPOINT INHIBITORS. If myocarditis is suspected, the clinician should: 1) withhold the checkpoint inhibitor; 2) organize an urgent admission to a monitored bed; 3) undertake a cardio-oncology evaluation with an electrocardiogram, transthoracic echocardiogram, biomarkers (ie, troponin I), and cardiac magnetic resonance imaging; 4) rule out acute coronary syndrome where appropriate; and 5) check for other adverse events associated with checkpoint inhibitors (ie, myasthenia gravis). If myocarditis is confirmed, the practitioner should, where appropriate: 1) treat any symptomatic heart failure, arrythmia, or conduction abnormalities; and 2) permanently cease treatment with immune checkpoint inhibitors. Please note this domain covered surveillance for myocarditis, not a specific treatment of confirmed myocarditis.

DISCUSSION

Attaining consensus for pediatric cardio-oncology guidelines in the acute setting has revealed the challenges that exist for cardiovascular disease risk-prediction and surveillance, where the evidence to date is largely focused on adult patients and off-

treatment survivors. Importantly, no studies in childhood cancer survivors (CCS) have been performed to assess whether more aggressive approaches to risk-factor management, above those recommendations for cardiovascular disease prevention for the general pediatric population, are necessary.[30] While many of the recommendations for high-risk patients at thresholds are known to predict cardiomyopathy in long-term CCS, it remains to be determined whether these risk factors confer risk in the acute setting, with the addition of novel therapies (molecular and immunotherapy) and whether cardio-oncology intense surveillance mitigates these risks. Nonetheless, our study creates an initial framework to review acute pediatric cardio-oncology clinics surveillance from which the impact of this surveillance on cardiovascular outcomes can be determined.

DEFINING A HIGH-RISK COHORT TO UNDERGO CARDIO-ONCOLOGY SURVEILLANCE. Some high-risk patient groups were quickly defined by the experts owing to the body of evidence available in pediatrics (ie, patients receiving ≥250 mg/m^2 of anthracycline [doxorubicin equivalent],[24] >15 Gy of irradiation with any dose of anthracycline [doxorubicin equivalent],[31] and >35 Gy of mediastinal irradiation[31]). Interestingly, other risk factors (ie, MS) took more than 1 round to reach consensus for high-risk inclusion and surveillance.

The association of hypertension, obesity (particularly central),[32] dyslipidemia, and diabetes, known as MS, is established as a risk factor for cardiovascular disease and death.[33] Importantly, MS can be diagnosed in pediatric cancer survivors at surprisingly short intervals following treatment completion. A French study of adolescents and young adult cancer survivors showed 9% of CCS met the criteria for an MS diagnosis at a median follow-up of 15.4 years from their cancer diagnosis.[34] The St. Jude's Lifetime Cohort Study (n = 1,598) revealed an even higher incidence of MS among CCS patients (31.8%, median follow-up 25.6 years). In this study, patients with MS were twice as likely to have abnormal global longitudinal strain and abnormal diastolic dysfunction on echocardiogram screening.[35] Current guidelines recommend screening for MS as part of late-effects screening. The Children's Oncology Group late-effects guidelines[28] recommend screening CCS who have received abdominal radiation or total body irradiation with fasting blood glucose or HbA1c every 2 years together with an assessment of height, weight, and blood pressure annually. Despite some studies reporting the necessity of screening on treatment for MS,[36] this has not been universally adopted. The consensus from the experts was not to mandate screening for MS during therapy, unless this is already a part of routine institutional practice. Of note, some patients may already be screened for dyslipidemia in routine cardiology follow-up. Patients who met the criteria for an MS diagnosis should undergo cardio-oncology screening.

Patients treated with new molecular targeted therapies and checkpoint inhibitors were also classified via consensus as high risk warranting cardio-oncology assessment. Adult harmonized guidelines identify elevated biomarkers prior to the anticancer therapy as an indication of high-risk patients warranting surveillance[27]; however, this was not perceived as relevant to the pediatric population unless incorporated in a clinical trial. Importantly, it was recognized that few patients will be on "active" therapy with the defined "high-risk" features. Patients meeting the definition of "high risk" who are in active therapy will likely relapse or be refractory or those receiving molecular or immune checkpoint inhibitors as part of first-, second- or third-line care.

DEFINING A MINIMUM SET OF CARDIO-ONCOLOGY INVESTIGATIONS. Domains 2 and 3 sought to define a minimum set of cardio-oncology investigations for high-risk patients, both generally and specific to their therapy. They also sought to define screening and surveillance approaches (including imaging and biomarkers), together with an assessment for the use of cardio-protection (ie, dexrazoxane).

The experts agreed that at the initial cardio-oncology review, an additional cardiovascular assessment should take place that includes a cardiac history of both the patient and their family (including a smoking history, from adolescence onwards). It was agreed that patient education and information should be provided in order to manage any modifiable cardiovascular risk factors (ie, obesity education, optimization of physical activity, healthy eating, and avoiding smoking), with re-emphasis at the end of therapy. Evidence suggests counseling for modifiable cardiovascular risk factors by treating practitioners is poor. For example, a survey by the Pediatric Cardio-Oncology Work Group of the American College of Cardiology[37] showed 48% of respondents routinely addressed blood pressure management, 46% routinely addressed diet and exercise, 46% addressed other cardiovascular issues (ie, smoking, obesity), and 14% never addressed any of the aforementioned conditions. Furthermore, 60% of respondents had never addressed exercise habits or marked this

domain as unknown in the survey. One of the opportunities raised by these recommendations is an opportunity to standardize earlier timepoints to address modifiable cardiovascular risk factors in patients receiving active therapy.

While the use of natriuretic peptides as early predictors of myocardial damage has been investigated in adult patients for some time, little testing has taken place in pediatrics. In this context, the experts were not in favor of implementing guidelines that mandated biomarker screening. Interestingly, the research for using biomarkers to detect cancer therapeutic-related cardiac dysfunction (CTRCD) in adult patients with cancer is also hampered by inconsistencies, leading to a discordance of opinion and approach. The European Society for Medical Oncology Guidelines, written for adult patients, support using troponin to detect and risk-stratify those at risk of CTRCD in the acute phases of cancer therapy.[38] However, a range of troponin levels to inform risk and provide guidance on management based on this risk is yet to be determined.[38] The Canadian Cardiovascular Society also recommend the serial use of biomarkers; however, they acknowledge that this is a weak recommendation.[19] Similarly, the American Society of Echocardiography recommend including biomarkers in baseline and subsequent assessments. If these biomarkers are abnormal, a cardiology consult is suggested.[39] To date, there has not been convincing demonstration of the diagnostic accuracy of cardiac biomarkers in routine surveillance as predictors of long-term CTRCD; however, it may be that we are not looking for the correct biomarkers currently.[40]

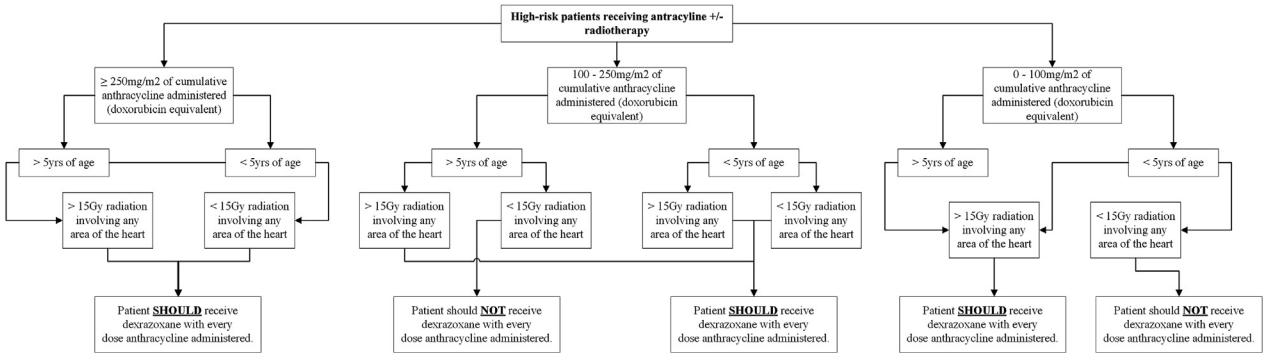
In pediatric oncology, larger cohorts are required to develop consensus regarding clinical standards for levels of blood-born biomarkers of cardiac distress, such as troponins and natriuretic factors. Lipshultz et al[41] investigated a cohort of pediatric patients with high-risk acute lymphoblastic leukemia for the trends in cardiac troponin T, N-terminal pro-brain natriuretic, and high-sensitivity C-reactive protein in patients receiving anthracycline. This study found that in the first 90 days of therapy, detectable increases in cardiac troponin T were associated with reduced LV mass and an LV end-diastolic posterior wall thickness 4 years later. However, the authors acknowledge that the study was not designed to determine biomarker cutoffs to inform clinical decisions or to determine the specificity or sensitivity of the biomarkers. To date, there has not been convincing demonstration of the diagnostic accuracy of cardiac biomarkers in routine surveillance as predictors of long-term CTRCD.[40] The expert opinion was that blood biomarkers for identifying at-risk on-treatment patients should form part of prospective clinical trials.

DEFINING MINIMUM CARDIO-ONCOLOGY SURVEILLANCE AND TREATMENT MANAGEMENT FOR CHEMOTHERAPY, MOLECULAR INHIBITORS, AND CHECKPOINT INHIBITORS. The experts defined guideline surveillance periods across new therapeutic groups (molecular inhibitors, checkpoint inhibitors). As part of these guidelines, we did not seek to be prescriptive about which expert group should lead the surveillance because of the heterogeneity of available services for cardio-oncology (Supplement). However, the experts did outline that their preference, where possible, was that patients were seen in cardio-oncology clinics or by specialists with expertise in cardio-oncology.

Consensus was met in the first round for screening toxicities (ie, blood pressure measurement, renal function, glucose level, lipid profile, electrocardiograms) specific to individual molecular inhibitors. However, routine screening for arterial thrombotic events related to BCR-Abl kinase inhibitor exposure was unsupported by the experts. BCR-Abl kinase inhibitors are associated with a range of cardiovascular toxicities (**Table 1**); the most serious of which are arterial thrombotic events. Adult cardio-oncology guidelines recommend that patients exposed to ponatinib receive peripheral artery disease screening by ankle brachial index measurement and Doppler ultrasounds of the supra-aortic and lower-extremity arteries.[27] In adult patients, an increased risk of arterial thrombotic events is more common in patients with additional cardiovascular risk factors and advanced age.[42,43] Studies of arterial thrombotic events in pediatrics are limited. For example, a multicenter case series in pediatric patients with chronic myeloid leukemia or Philadelphia positive acute lymphoblastic leukemia treated with ponatinib enrolled 21 patients across a short follow-up period (median 3 months, range 4 days-66 months) and showed no patients experienced symptomatic arterial thrombotic events.[44] Importantly, in adult studies, the median time to experiencing a serious symptomatic arterial thrombotic event was 3 to 6 months,[43,45] which is beyond the median follow-up time of the study by Rossoff et al.[44] The consensus from the experts was that surveillance for asymptomatic arterial thrombotic events should be performed as part of pilot cardio-oncology trials.

One of the most important and recurring questions arising in pediatric oncology is how to manage poor or declining LV function. In this domain, we aimed to understand if treating physicians would currently recommend the use of heart failure medications (ie,

FIGURE 3 Recommendations for Review and Use of Dexrazoxane Cardioprotection in Patients Exposed to Anthracycline and/or Radiotherapy



ACE inhibitors or beta-blockers) for patients with LVEF between 40% and 50% and, similarly, in patients with LVEF ≤40%. Consensus for using heart failure medications in patients with documented LVEF ≤40% was met in the first round. However, the use of heart failure medication for LVEF declining 50% to 40% did not reach a consensus opinion, which reflects the paucity of available evidence. The ACE Inhibition After Anthracycline study examined whether an ACE inhibitor (enalapril) could lower the rate of decline of cardiac function, in a cohort of CCS.[46] The study was unable to answer the proposed hypothesis for a range of reasons including: 1) follow-up time of participants was too short; 2) the limited number of study patients; and 3) the study was inaccurately powered to rule out a clinically relevant effect of enalapril.[47] Lipshultz and Colan ran a long-term study of CCS in the same era, with randomization of patients to enalapril or placebo (Pediatric Oncology Group trial 9480), and were forced to close the study prematurely because of poor enrolment. The proposed value of ACE inhibition in patients suffering from anthracycline-induced cardiac disease was based on ACE inhibition efficacy in dilated cardiomyopathy of alternate etiologies. Lipshultz and Colan[47] argue that anthracyclines produce predominantly a restrictive cardiomyopathy, and thus, the benefits of ACE inhibition should be limited. To date, the question of whether ACE inhibition carries a morbidity or mortality benefit to anthracycline-exposed CCS remains unanswered. Lipshultz and Colan have commented that such a trial would be expensive to design and needs to run across many decades given the natural history of the disease, which is difficult when introducing a therapy that is not without its own side effect profile. Despite these initial studies in CCS being performed 2 decades ago, there have not been further advances in the field to prove the benefit of ACE inhibition in pediatric oncology patients.[48] Of note, the American Heart Association adult guidelines do recommend treatment with ACE inhibition for symptomatic patients with an EF <50.[49]

Currently, dexrazoxane is the sole cardioprotective agent used in pediatric oncology. This iron chelator has a role in preventing cardiotoxicity in cancer survivors, although conclusive evidence has not yet been demonstrated by a Cochrane review.[50] The literature does not recommend its use in patients who are at low risk of developing cardiomyopathy or in patients receiving liposomal anthracyclines.[51] The experts unanimously agreed that patients receiving ≥250 mg/m^2 of a doxorubicin equivalent are considered to be at high risk of developing cardiomyopathy and should be offered dexrazoxane. Interestingly, defining other risk groups should receive dexrazoxane was more difficult with a broad concern about lack of data to support dexrazoxane use. While dexrazoxane has been demonstrated to be safe when used in a 10:1 ratio (doxorubicin equivalence), its efficacy at preventing cardiac death or morbidity is yet to be conclusively demonstrated. Internationally, some centers are recommending that patients considered to be at a moderate risk of developing cardiomyopathy (ie, those with 100-250 mg/m^2 of an doxorubicin equivalent dosing, or any chest radiotherapy in combination with any anthracycline dose) should be considered for dexrazoxane dosing, particularly if their disease has a high likelihood of relapse. Overall, the experts identified that further evidence on efficacy and health economic analysis was necessary prior to broadening inclusion criteria for dexrazoxane use to medium-risk or indeed low-risk patients. Recommendations for use of dexrazoxane as cardioprotection in patients exposed to anthracycline and/or radiotherapy can be found in **Figure 3**. The role of pharmacogenomic predisposition to chemotherapy

toxicity including anthracyclines and cardiotoxicity is still an emerging topic in pediatric oncology.[52] In future years, there may be enough evidence to recommend pre-emptive genetic screening and alternate cardio-oncology surveillance for this cohort of patients; however, this was beyond the scope of these consensus guidelines.

STUDY LIMITATIONS. One of the limitations of our study was the starting point of the Delphi survey being adult cardio-oncology guidelines. We chose this starting point as they were the only ones that address acute cardio-oncology care relevant to the plethora of molecular and immune checkpoint inhibitors unavailable in the current pediatric oncology guidelines. In addition, there are limited studies to date that investigate whether pediatric patients (who arguably carry less comorbidities) carry the same risk of cardiovascular adverse drug reactions in the acute setting with modern therapeutics. Further limitations include that the experts for this Delphi were all from Australia and New Zealand. It is possible that experts from different continents, who practice in differently resourced and organized health care systems, may have reached an alternate consensus. The expert consensus would also have been influenced by the presence or absence of cardio-oncology programs and integration of cardiologists within pediatric oncology care.

CONCLUSIONS

The advent of cardio-oncology as a subspecialty opens the opportunity to develop a standardized practice for pediatric oncology patients across a range of cardiotoxic complications observable in the modern time. We have observed, through the expert consensus approach, the absence of evidence-based literature around the benefit of acute screening and the potential impact on long-term cardiovascular outcomes. We have sought to address this gap in knowledge by provision of an expert consensus framework for: 1) defining a high-risk group of patients who should undergo cardio-oncology assessment; 2) standardizing an approach to screening and surveillance during an acute therapy; 3) recommendations for cardio-protection; and 4) opportunities for formal cardio-oncology research studies to further strengthen the evidence base available.

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APPENDIX For supplemental information, please see the online version of this paper.