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ARTICLE TITLE

Cardiovascular and pulmonary challenges after treatment for Childhood Cancer

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KEY WORDS

Late effects, childhood cancer survivor, cardiovascular, pulmonary

KEY POINTS

List 3 to 5 key points of approximately 25 words each that summarize the main points of the article. Key points appear beneath the article title and authors in print and online

- Cardiovascular and pulmonary disease are the second leading non-recurrence causes of death in childhood cancer survivors
- Anthracyclines and radiotherapy to heart, head and neck cause substantial cardiovascular disease, particularly congestive heart failure, ischemic and valvular heart disease, and stroke
- Bleomycin, busulfan, nitrosureas, chest radiation and lung surgery are the main contributors to pulmonary disease
- Prevention and regular screening according to established are crucial as treatment options are limited once disease becomes clinically manifest
- Childhood cancer survivors should be encouraged to adopt healthy lifestyles (exercise, healthy diet, no smoking) and modifiable risk factors should be addressed

SYNOPSIS

Provide a brief summary of your article (100 to 150 words; no references or figures/tables). The synopsis appears only in the table of contents and is often used by indexing services such as PubMed

Childhood cancer survivors are at increased risk for developing cardiovascular as well as pulmonary disease related to their cancer treatment. This might not become apparent until many years after treatment and it can vary from subclinical to life threatening disease. Most important causes are anthracyclines and radiotherapy involving heart, head or neck for cardiovascular disease, and bleomycin, busulfan, nitrosureas, radiation to the chest, and lung or chest surgery for pulmonary disease. Most of these effects are dose-dependent, but genetic risk factors have been discovered in particular for anthracycline cardiotoxicity. Treatment options once disease becomes clinically manifest are limited. Prevention and regular screening according to established follow-up guidelines are crucial and survivors should be encouraged to adopt a healthy lifestyle and modifiable risk factors should be addressed.

Cardiovascular and pulmonary challenges after treatment for Childhood Cancer

Introduction

Both cardiovascular and pulmonary disease occur with increased frequency in childhood cancer survivors (CCS), although both might not become apparent until many years after treatment.[1] These late effects of cancer therapy can vary from subclinical to life threatening and can substantially increase mortality and morbidity. In fact, after subsequent malignancies, cardiovascular and pulmonary disease are the leading non-recurrence causes of death in CCS.[2-4]

In particular, there is a 5 to 10-fold increase in mortality due to cardiovascular disease[2-4], which is in large part due to the 5 to 15-fold increased risk of congestive heart failure (CHF)[5], and more than 10-fold increased risk of ischemic heart disease and stroke.[6] Similarly, the risk of death from a pulmonary event is 7 to 14 times higher in CCS compared to the general population[2,7,8], and hospitalization due to respiratory conditions is 2 to 5 times higher in survivors.[9-11]

The purpose of this review is to describe the current knowledge of cardiac and pulmonary late effects including risk factors, early detection, possible treatments and opportunities for prevention.

Cardiovascular disease

Cardiovascular disease (CVD) after childhood cancer usually manifests as left ventricular (LV) systolic dysfunction/heart failure, ischemic (coronary artery) heart disease, or stroke.[1,12-15] However, patients can also develop pericardial disease, arrhythmias, or valvular and peripheral vascular dysfunction.[13,16] Both chemotherapy and radiotherapy can contribute to these conditions either alone or in combination. For example, in a study of 5,845 CCS, those who received both cardiotoxic chemotherapy and radiotherapy involving the heart (7%) had a cumulative incidence of heart failure 40 years after diagnosis of 28%, whereas patients who received only cardiotoxic chemotherapy or only radiotherapy involving the heart had a cumulative incidence of 11% and 3%, respectively.[17]

Risk factors and pathophysiology

The increased risk of cardiovascular disease in CCS is mainly due to exposure to anthracyclines and radiotherapy involving the heart.[4-6,13,18] However, other conventional chemotherapeutic drugs, radiotherapy to head and neck, and a growing list of newer targeted agents that are increasingly being used in children can all affect this risk (Table 1).[4,6,13,15,16,18-21] In addition, standard risk factors for CVD

such as hypertension, dyslipidemia, diabetes mellitus and obesity, many of which are more prevalent in CCS, contribute to the increased CVD risk.[22-24]

Conventional chemotherapy

Anthracyclines (e.g. doxorubicin, daunorubicin, idarubicin, epirubicin) including the anthraquinone, mitoxantrone, are commonly used to treat a variety of childhood cancers, and have been known for several decades to cause dose-dependent cardiotoxicity that can range from subclinical with only mildly reduced shortening fraction[25,26] to severe overt clinical heart failure.[13,17,27]

Anthracycline cardiotoxicity (ACT) has historically been described based on the time of onset, which can be acute, early (within the first year of treatment) or late (after the first year). Though early onset ACT can resolve without intervention, some patients continue to have left ventricular systolic dysfunction which might be progressive, whereas others develop late onset ACT after a latency period free of symptoms, suggesting this might a continuum rather than clearly different entities and that additional myocardial injury or stress might contribute to developing later symptoms.[28-30]

The effects of anthracyclines are dose-dependent and increase over time with CCS who received a cumulative doxorubicin-equivalent dose ≥250 mg/m^2 having a 30-year follow-up cumulative incidence of CHF of 8-13%.[17,27] Not all anthracyclines are equally cardiotoxic with mitoxantrone carrying the highest risk for CHF and hence the conversion into doxorubicin-equivalents.[31] Patients who were younger during the exposure and, though not consistently, females also seem to be at higher risk.[5,17,27]

Despite being studied extensively, the exact mechanism of anthracycline toxicity has not been fully unraveled. Many preclinical studies have focused on redox cycling of anthracyclines and generation of reactive oxygen species (ROS) with cardiomyocytes being particular susceptible to ROS[32], whereas others have found mitochondrial iron accumulation to be involved.[33] Another important mediator of ACT is topoisomerase IIb (Top2b): cardiomyocyte-specific deletion of this gene, which is one of the forms of topoisomerase 2, the presumed cellular target of doxorubicin, protects mice from doxorubicin cardiotoxicity.[34] Interestingly, several of genetic risk factors for ACT that have been found (see below) are in genes related to ROS and iron metabolism or that interact with Top2b.

Alkylators are another large group of drugs commonly used in childhood cancer or hematopoietic stem cell transplantation (HSCT), of which some have been associated with different types of CVD. Most of these toxicities were initially reported in adults, but can occur in children.[16,35] In particular, cyclophosphamide at higher doses, such as in myeloablative HSCT conditioning, can cause acute myocarditis with subsequent left ventricular systolic dysfunction and acute CHF, though most patients

recover.[16,35] Similarly, ifosfamide can cause CHF as well as arrhythmias. More recently, cyclophosphamide, but not ifosfamide was found to be associated with CHF in long-term CCS.[17] Another study linked cyclophosphamide to pericardial disease, but not CHF.[27] Alkylators were also associated with a higher risk of stroke[6,19,36], though this might be limited to certain subgroups, such as patients with brain tumors.[15,19,37]

Antimetabolites. Case reports in adults have noted pericarditis, arrhythmias, and CHF after high doses of cytarabine.[35] Cytarabine is frequently used in children. It is unclear how often, if at all, cardiotoxicities occur and what the long-term outcomes are. Similarly, the anti-metabolite 5-fluorouracil, though only occasionally used in children, has been linked to ischemic heart disease, arrhythmias, and heart failure including in some pediatric case reports.[16]

Platinums, specifically cisplatin, has been found to cause arrhythmias, possibly through electrolyte disturbances.[35] In addition, vascular dysfunction, either through vasospasm or endothelial damage and platelet aggregation, can lead to myocardial infarction and stroke.[6,16,35]

Vinca alkaloids such as vincristine and vinblastine seem to increase risk for ischemic heart disease in adults.[38] Results in CCS are more conflicting; one study found an increased risk of cardiovascular death after vinca alkaloid exposure[4], whereas others failed to find such an association[13,17] or found even lower risk of myocardial infarction.[27] Possibly, the increased CVD death could be due to the often concomitant exposure to alkylators.[4]

Radiotherapy

Radiation involving the heart has been known for decades to cause ischemic heart disease, pericardial and valvular disease and radiotherapy can also increase the risk of anthracyclines induced heart failure.[5,6,13,17,27] Arrhythmias are also common, but might occur only after longer follow-up. These effects are also dose-dependent with patients treated with higher doses, in particular those ≥35 Gy, being at highest risk.[5,6,27]

Radiation to head and neck have both been consistently associated with stroke in CCS, including transient ischemic attacks, cerebral infarction and intracranial hemorrhage.[6,15,19,37] Again, this effect is dose-dependent, with patients receiving ≥30 Gy to the brain at highest risk, in particular patients treated for brain tumors.[6,19] The risk of stroke increases over time and can be as high as 20% in high risk patients by age 50.[6,15,19] The toxic effect of radiotherapy is presumed to be through the cerebral vasculature, with radiation causing an inflammatory response in the vessel wall leading to luminal narrowing and weakening of the wall that can over time result in occlusion or hemorrhage.[14]

New targeted agents

Better understanding of the biology and molecular pathways involved in cancers, has led to the discovery and use of many new targeted agents, which have revolutionized the treatment of some cancers. While these agents were developed against cancer-specific molecules or aberrant pathways, many have specific toxicities both on-target/off-tumor (target also expressed elsewhere) as well as off-target (drug not specific for the target) including the cardiovascular system.[20] As some of these agents are increasingly being used in children, the long-term impact of these toxicities in CCS needs to be considered, especially as these agents are given in addition to conventional treatments.[21]

BCR-ABL directed tyrosine kinase inhibitors (TKIs) such as imatinib, but also the newer dasatinib and ponatinib, are commonly used in pediatric Philadelphia (Ph) positive acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML) and block the BCR-ABL fusion gene kinase. Especially newer TKIs have been associated with a variety of CVD toxicities including LV dysfunction/cardiomyopathy, ischemic heart disease, stroke and vascular disease.[39] While they were primarily developed for targeting BCR-ABL, they are in fact multi-kinase inhibitors that also affect kinases in the cardiovascular system, in particular anti-VEGF (see below), which might explain this toxicity.[39] As some patients require long-term treatment with TKIs (e.g. CML, Ph+ ALL), these toxicities are becoming more important.

Immune checkpoint inhibitors restore antitumor immunity by blocking inhibitory signals or receptors on tumors or immune cells such as PD-1, PD-L1 or CTLA-4.[40] Commonly used in adults, drugs such as nivolumab, ipilimumab and pembrolizumab are studied and used in children.[21] However, blocking the inhibitory pathways can shift the balance towards autoimmunity including myocarditis with associated heart failure, which carries a high fatality rate.[40]

Proteosome-inhibitors have been found to cause heart failure, ischemic heart disease and arrythmias, although this risk might be lower for bortezomib, which is used for pediatric relapsed or refractory ALL.[20]

VEGF-inhibitors or **TKIs with anti-VEGF activity** can have various cardiovascular toxic effects similar to BCR-ABL directed TKIs. VEGF-inhibitors such as bevacizumab, used in certain central nervous system (CNS) tumors (e.g. gliomas), inhibit tumor angiogenesis by directly blocking VEGF, whereas the anti-VEGF effect of TKIs, including FLT3-inhibitors, such as sorafenib used in certain high risk acute myelogenous leukemia (AML) patients, is off-target.[41] Cardiovascular toxicity include thromboembolic events leading to ischemic heart disease and stroke, cardiomyopathy with heart failure, which is partly mediated through an increased risk of hypertension.[20,41] These toxicities are important in CCS, especially for AML patients, who often receive anthracyclines and FLT3-inhibitors.

Genetic risk factors

In addition to exposure to specific therapies, certain germline genetic variations have also been found to modify CVD risk, in particular for ACT. Studies that focused specifically on ACT in CCS have found variants in genes related to anthracycline transport and metabolism (*SLC28A3*[42,43], *UGT1A6*[42,43], *CBR3*[44,45], *SLC22A7*[46], *SLC22A17*[46], *ABCC5*[47]), iron metabolism (*HFE*[48]), oxidative stress (*CAT*[49], *GSTP1*[50], *NOS3*[47], *HAS3*[51]), hypertension (*PLCE1*[52], *ATP2B1*[52]), cardiac physiology or structure (*HAS3*[51], *CELF4*[53], *GPR35*[54], *TTN*[55]), and DNA damage (*RARG*[56]). Some variants have been replicated in multiple cohorts, while others have not, and the functional consequences of these variants have only been partly explored.[57]

Diagnosis, surveillance, treatment and prevention

Echocardiography remains the mainstay for screening and diagnosis of cardiac disease in CCS, and in particular for LV dysfunction after anthracyclines and chest RT, measuring shortening or ejection fraction (EF).[58] Echocardiography can also diagnose valvular abnormalities, diastolic dysfunction, and pericardial disease. When more sensitive parameters such as global longitudinal strain are used, echocardiography can detect more subclinical systolic dysfunction than by measuring EF alone.[59] Cardiac magnetic resonance imaging (MRI) is even more sensitive, but is also more costly and not readily available in every center.[58] Imaging to detect vascular or cerebrovascular disease are not routinely used to screen asymptomatic CCS.

Currently, international harmonized guidelines provide recommendations for screening for cardiomyopathy in CCS using echocardiography.[58] Further refinement of risk for CVD using clinical risk factors[5,6] or incorporating genetic variants[60] might aid to decide which CCS to screen and how often, thereby likely improving screening cost effectiveness.[58,61,62]

Electrocardiography at baseline is recommended by most CCS long-term follow-up guidelines[61,62], but its role to detect conduction abnormalities in asymptomatic CCS is unclear.[63]

Cardiac biomarkers such as troponins or the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) have been studied extensively in CCS, but while elevations of these markers during treatment might predict long-term LV dysfunction, their role for screening asymptomatic survivors is limited due to their low sensitivity.[58,64] Of course, these markers may be used to monitor or screen symptomatic patients similar to the general population.[58]

Prevention

To prevent cardiovascular toxicities from occurring, treatment protocols have evolved over time reducing, omitting or replacing certain chemotherapeutic agents and radiotherapy without affecting cancer treatment outcome. For example, maximum cumulative doses for anthracyclines are recommended in many protocols and radiotherapy has successfully been reduced in the treatment of Hodgkin Disease.[16] Risk prediction models might identify patients who will benefit most from these preventative measures.[5,6,57,60] Newer radiation techniques including Intensity-Modulated Radiation Therapy (IMRT) or proton therapy might further reduce the harmful effects to cardiovascular structures.[16] Cardioprotective agents, specifically dexrazoxane, have been studied extensively and dexrazoxane seems to reduce ACT without affecting anti-tumor efficacy or increasing secondary malignancies.[65]

Secondary prevention, aimed at preventing CVD after treatment exposures, relies in part on screening and early detection of subclinical disease to initiate pharmacologic treatment as mentioned above for heart failure. In adult cancer survivors, the combination of ACE-inhibitors and ß-blockers was shown to help recover cardiac function after early detection of LV dysfunction, even in asymptomatic survivors.[30] Though while the role of pre-emptive heart failure treatment in asymptomatic CCS is less clear, it is still often employed.[16,66] Other strategies focus on targeting modifiable risk factors such as hypertension, dyslipidemia, diabetes mellitus and obesity and adopting a healthy lifestyle (i.e. regular exercise, healthy diet, no smoking)[16,24], which have been incorporated in survivor guidelines.[61,62]

Treatment

Treatment for CVD in CCS depends on the type of disease and is usually managed similar to the general population.[16] CCS with heart failure are commonly treated with angiotensin converting enzyme (ACE) inhibition often in combination with ß-blockers, though the evidence in children is scarce.[16,67,68] Importantly, once symptoms occur, heart function can rapidly decline and become refractory to treatment necessitating mechanical support or heart transplant.[16]

Pulmonary disease

Pulmonary disease is another important long-term complication in CCS with high morbidity and mortality. This is due to a range of pulmonary conditions, such as fibrosis, emphysema, recurrent pneumonia, or chronic cough that affect survivors throughout their life and increase in frequency with longer time elapsed from cancer treatment.[1,69,70]

Risk factors and pathophysiology

Several important treatment modalities, such as bleomycin, busulfan, lomustine (CCNU) or carmustine (BCNU), radiation of the thorax, and surgery to the lung or chest wall, impart a risk of pulmonary damage. Patients after HSCT are at particular risk because their treatment often incorporates more than one treatment-related risk factor. Unlike in CVD, no studies have systematically investigated genetic risk factors for pulmonary toxicity.

Chemotherapy

For most categories of chemotherapeutic agents and their combinations, reports of chemotherapy-induced lung injuries have been published; although, often only as case reports or case series. Consistent and robust evidence for pulmonary toxicity is available for bleomycin, busulfan, and nitrosureas (BCNU, and CCNU).[71-73]

Bleomycin is used to treat Hodgkin lymphoma and germ cell tumors. The lung is vulnerable to this agent because it lacks the bleomycin-inactivating enzyme bleomycin hydrolase. This leads to free radical formation and oxidative damage to lung tissues. Subsequent inflammatory processes eventually cause alveolar damage, hypersensitivity reaction, pneumonitis, and pulmonary fibrosis (Table 2). Reported prevalence of bleomycin-induced pneumonitis (BIP) ranges from 0-46%. BIP usually develops during treatment, resulting in cough, dyspnea, and fever.[74] Data on long-term prognosis after BIP are inconsistent. One review concluded that radiographic changes and lung function abnormalities usually resolve completely.[74] However, two studies that assessed lung function by spirometry, body plethysmography, and measurement of diffusion capacity for carbon monoxide (DLCO) in children, 2 and 4 years after exposure to bleomycin, found that 41% and 52% of children respectively had pathological test results at these time points.[75,76] The toxicity is dose dependent and more common with doses >400U/m2, which are seldom used in pediatrics. Simultaneous or subsequent radiotherapy to the lung, exposure to elevated oxygen concentrations, renal dysfunction, smoking, and higher age at treatment may exacerbate bleomycin toxicity.[72,74,77]

Busulfan is an alkylating agent used mainly to condition children before autologous or allogeneic HSCT. The exact mechanism of lung injury is unknown, and the dose-response relationship is unclear. However, it seems that cumulative doses <500 mg do not cause pulmonary injury in adults.[72,73,78] As with bleomycin, concomitant irradiation may magnify the toxic effect of busulfan.[72]

Nitrosureas, including CCNU and BCNU, are mainly used to treat brain tumors and to condition patients for autologous HSCT. Nitrosureas are risk factors for pneumonitis and pulmonary fibrosis (Table 2). Pulmonary fibrosis usually develops slowly over years or decades with asymptomatic periods of various length.[79] In nitrosurea-induced pulmonary fibrosis, inflammatory reactions followed by depletion of Type I pneumocytes and hyperplasia of Type II pneumocytes lead to increased collagen deposition.[80] Higher cumulative doses are associated with increasing risk of lung injury. Patients exposed to thoracic irradiation may develop lung injury at lower doses of nitrosureas than those not exposed.[72,73,81] A case series followed 17 long-term brain tumor survivors treated with high-dose BCNU and spinal irradiation (n=12) for up to 25 years. Half (53%) of the survivors died of pulmonary fibrosis. All seven patients still alive and in follow-up after 25 years showed radiologic and physiologic (i.e. lung function) evidence of pulmonary fibrosis.[79,82]

Radiotherapy

Direct irradiation of the lung, but also scattered radiation after radiotherapy to the chest wall, abdomen or spine increase the risk for pulmonary damage. Radiation can lead to DNA strand breaks and trigger lung injury by starting a cascade of inflammatory reactions, with capillary leaks and alveolar and interstitial exudate, which later organizes into collagen. Acute radiation pneumonitis usually develops within 6 weeks to 3 months after radiotherapy (Table 2). The most frequent symptoms are dyspnea and cough. Although early stages of radiation pneumonitis can be self-limited and resolve completely, most patients develop progressive fibrosis.[80] Toxicity due to radiation depends on the irradiated lung volume, the total dose, the method of irradiation, such as dose fraction, and the application of radiosensitizer. At least 10% of the lung volume has to be irradiated to produce significant toxicity. Radiation pneumonitis rarely develops in cases of fractionated radiotherapy with a total dose <20Gy, but is common if the cumulative dose exceeds 40-60Gy.[71,73,83,84]

Surgery

Extensive pulmonary and chest wall surgery can alter pulmonary function.[85] Lobectomy or resection of multiple metastases leads to reduced lung volumes. Removal of ribs or part of the chest wall can

cause restrictive ventilation impairment due to a reduction in expansibility of the chest wall.

Hematopoietic stem cell transplantation (HSCT)

Children treated with HSCT face transplant-specific pulmonary complications and late effects in addition to those mentioned above. About 37% of patients after HSCT develop pulmonary complications.[86] Pulmonary complications are divided in infectious and non-infectious depending on the underlying cause. The non-infectious complications are generally transplant-specific, such as Bronchiolitis Obliterans Syndrome (BOS), diffuse alveolar hemorrhage (DAH), and idiopathic pneumonia syndrome (IPS) (Table 2). DAH and IPS typically present with an acute onset of respiratory failure within the first 30 days and 120 days after HSCT respectively.[86] Both diseases have a high mortality, but no data on long-term outcomes exist.[86] BOS is typically diagnosed >100 days after transplantation.[86,87] The main symptoms of BOS are dry cough and dyspnea. BOS has a variable clinical course, but most patients have slowly progressive airflow obstruction. Stabilization or improvement of lung function is rare.[87]

Diagnosis, surveillance, treatment and prevention

Lung function tests

Lung function impairment in childhood cancer survivors is assessed by pulmonary function tests. Pulmonary symptoms such as chronic cough or dyspnea at exertion are late signs of pulmonary dysfunction. One study found that only 24% of those with restrictive disease diagnosed by lung function tests reported symptoms using the Medical Research Council Dyspnea Questionnaire.[88]

Lung function is usually assessed by spirometry, body plethysmography, and measurement of the diffusing capacity for carbon monoxide (DLCO), with restrictive, obstructive, mixed restrictive-obstructive patterns and decreased diffusion capacity having been reported. Decreased diffusion capacity is the most frequent abnormality (35-45%), followed by restrictive (13-32%) and obstructive disease (1-4%).[75,76,88-91] Few studies have assessed lung function longitudinally, so that knowledge on long-term prognosis is scarce. Repeated lung function tests in survivors after HSCT found three phases in lung function trajectories: 1) an initial decrease in lung function after completion of treatment, lasting for 3-6 months; 2) a subsequent recovery until 1-2 years after completion, usually not reaching baseline values; 3) stable values or slow deterioration in the long-term follow-up.[92-94]

Multiple breath washout tests (MBW) might be more sensitive to identify early changes. They measure ventilation inhomogeneity in the lung, which is increased in case of central and peripheral airway

obstruction. One study assessed pulmonary function in adults (n=225) with BOS following HSCT with MBW and found the test to be highly sensitive for detecting abnormal lung function in their cohort (95% abnormal MBW test compared to 56% abnormal FEV1/FVC).[95] Whether this test will be valuable in the early detection of lung function impairment in CCS must still be evaluated. Additional examinations, such as imaging or lung biopsy, are used in case of suspected pulmonary disease but not in regular follow-up care.

Surveillance

National and international follow-up guidelines concerning pulmonary late effects specify that the use of the chemotherapeutic agents mentioned above, radiotherapy to the chest, and thoracic surgery are indications for pulmonary follow up using lung function tests.[61,62,96] However, the available evidence is scarce, and the effect of other chemotherapies unclear, so more dedicated research is needed.

Treatment and prevention

Treatment options for pulmonary diseases and functional impairment in CCS depend on the underlying disease. In general, treatment options are limited but the field is evolving quickly. Here, we focus on treatment options for non-infectious pulmonary diseases beyond the acute phase. BOS can be treated with systemic steroids, but these can increase the risk of pulmonary infection.[97,98] Inhaled bronchodilators do not improve pulmonary function in these patients.[98] One case series reported that patients with BOS who received inhaled fluticasone, azithromycin, and montelukast (FAM) could reduce their doses of systemic steroids compared to those not treated with FAM, thereby sparing them from the serious toxicities associated with long-term steroid use.[98] The subsequent phase II study confirmed that the FAM-regimen with reduced doses of systemic steroids was well tolerated and resulted in a reduction in pulmonary function decline in most patients.[99] Systemic steroid therapy improves radiation pneumonitis, but most experts agree that corticosteroid therapy is ineffective for the treatment of pulmonary fibrosis.[71,73] A few newer drugs, such as the TKI nintedanib, are available for adults with idiopathic pulmonary fibrosis. Data for the use in children are lacking. Nintedanib slows lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.[100,101]

Because treatment options are limited, prevention of pulmonary damage has high priority. Bleomycin is no longer a first-line therapy for lymphoma, though remains a core component of germ cell tumor therapy, and radiotherapy has been reduced in many protocols, but avoidance of pulmonary toxic chemotherapy or radiation is not always possible. Therefore, any additional damage to the lung should

be avoided throughout the survivors' life. Survivors must be counselled not to smoke and to avoid second hand smoke exposure. Pneumococcal and influenza vaccination should be considered in survivors with established pulmonary disease. Survivors should be advised to inform anesthetists about previous bleomycin treatment in case of general anesthesia, because high inspired oxygen (FiO2>30%) concentration may further affect preexisting pulmonary damage.[102] Also survivors who desire to scuba dive should have a pulmonary consultation prior to undertaking the activity.[61,62,96]

Conclusion

Cardiovascular and pulmonary disease after childhood cancer treatment impose great challenges for survivors. The cardiovascular system and lungs can be severely affected by cancer treatment in many ways resulting in increased morbidity and mortality. Treatment options once disease becomes clinically manifest are focused to decrease symptoms but will not cure cardiovascular or pulmonary disease. Therefore, prevention and regular screening according to established follow-up guidelines are crucial even in the absence of symptoms, which generally occur rather late. Survivors should be encouraged to adopt a healthy lifestyle and modifiable risk factors should be addressed. Close collaboration and early referral to experienced specialists (e.g. cardiologist, pulmonologist) is essential for optimal diagnosis and management.

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Table 1: List of treatments for childhood cancer associated with cardiovascular disease

Treatment modality	Late effect/disease	References
Chemotherapy		
Anthracyclines (e.g. doxorubicin, daunorubicin, idarubicin, mitoxantrone)	LV systolic dysfunction/heart failure, pericardial disease, arrhythmia	5,13,17,25-28
Alkylators (e.g. cyclophosphamide, carmustine, lomustine, ifosfamide)	Stroke, LV systolic dysfunction/heart failure, pericardial disease, arrhythmias	6,15-17,19,27,35-37
Antimetabolites (e.g. cytarabine, 5-FU)	Pericardial disease, arrhythmias, ischemic heart disease, heart failure	16,35
Platinums (e.g. cisplatin)	Stroke, arrhythmias, vascular disease, ischemic heart disease	6,16,35
Vinca alkaloids (e.g. vincristine, vinblastine)	Ischemic heart disease	4,38
Radiotherapy		
Chest (heart)	Ischemic heart disease, valvular disease, pericardial disease, arrhythmia, heart failure	5,6,13,17,27
Head/neck	Stroke	6,15,19,37
New targeted agents		
BCR-ABL TKIs (e.g. imatinib, dasatinib, ponatinib)	LV systolic dysfunction/heart failure, arrhythmias, ischemic heart disease, stroke, vascular disease	39
Immune checkpoint inhibitors (e.g. nivolumab, ipilimumab, pembrolizumab)	Myocarditis, heart failure	21,40
Proteasome-inhibitors (e.g. bortezomib)	Heart failure, ischemic heart disease, arrythmias	20
VEGF-inhibitors or TKIs with anti-VEGF activity (e.g. bevacizumab, sorafenib)	Vascular disease, ischemic heart disease, stroke, cardiomyopathy/heart failure	20,41

Table 2: List of treatments for childhood cancer associated with pulmonary disease

Treatment modality	Late effect/disease	References
Chemotherapy		
Bleomycin	Acute respiratory distress syndrome (ARDS) Interstitial or hypersensitivity pneumonitis Bronchiolitis obliterans organizing pneumonia (BOOP) Pulmonary veno-occlusive disease (VOD) Pulmonary fibrosis	72-76
Busulfan	Acute respiratory distress syndrome (ARDS) Alveolar proteinosis Pulmonary fibrosis	72,73,78
Nitrosureas (Carmustine, Lomustine)	Hypersensitivity pneumonitis Alveolitis Pulmonary veno-occlusive disease (VOD) Pulmonary fibrosis	72,73,79,81,82
Radiotherapy to the chest	Bronchiolitis obliterans organizing pneumonia (BOOP) Interstitial pneumonitis Impaired chest wall growth Pulmonary fibrosis	71-73,83,84
Surgery (e.g. pulmonary lobectomy, pulmonary wedge resection, pulmonary metastasectomy, chest wall resection)	Restrictive lung function impairment Scoliosis Chest wall deformity	72,85
Stem cell transplantation Lung toxic agents used for conditioning	See agents above	
Transplant-specific non-infectious pulmonary complications	Idiopathic pneumonia syndrome (IPS) Bronchiolitis obliterans syndrome (BOS) Bronchiolitis obliterans organizing pneumonia (BOOP) Diffuse alveolar hemorrhage (DAH)	72,86,87