Pulmonary System

8

Tara O. Henderson

8.1 Introduction

Pulmonary disease is a highly prevalent cause of premature morbidity and mortality in long-term childhood cancer survivors. In the large-scale retrospective North American cohort, the Childhood Cancer Survivor Study (CCSS), Armstrong and colleagues reported significant excess rates of death due to pulmonary disease (standard mortality ratio, 8.8), second only to death from second malignant neoplasms [1]. Pulmonary toxicity is frequently reported in survivors of Hodgkin lymphoma, germ cell tumors, acute lymphoblastic lymphoma and metastatic Wilms tumor survivors, as the chemotherapy, radiation and surgeries used to treat these pediatric cancer (among others) can result in permanent lung damage [2, 3]. This damage can manifest as acute pneumonitis, late onset fibrosis, and structurally induced dysfunction from developmental abnormalities due to impaired growth of the thorax attributable to surgery or radiation. The cumulative incidence of pulmonary problems after childhood cancer increases with time since diagnosis, as with other late-effects, suggesting that survivors are at an elevated risk of developing later-onset pulmonary morbidities as they age [4].

T.O. Henderson, M.D., M.P.H. (✉)
Comer Children's Hospital at the University of Chicago, 5841 S. Maryland Avenue, MC 4060, Chicago, IL 60637, USA
e-mail: thenderson@peds.bsd.uchicago.edu

8.2 Radiation-Induced Pulmonary Damage

The lungs are particularly sensitive to radiation. Pulmonary late effects occur most often in patients with malignant diseases of the chest that are treated with radiation, i.e., those involving the mediastinum, the lung parenchyma or the chest wall. These survivors typically include those treated with chest or mantle field radiation for Hodgkin lymphoma, non-Hodgkin lymphoma, or sarcoma, and those whose primary disease metastasized to the lung (i.e., Wilms tumor). In one of the largest studies of pulmonary outcomes among adult childhood cancer survivors exposed to pulmonary toxic therapy, Mulder and colleagues demonstrated that radiation was the most important risk factor for pulmonary late effects [5]. In those exposed directly or indirectly to lung radiation, abnormal radiographic findings or restrictive changes on pulmonary function testing have been reported in more than 30 % of patients. In addition to radiation dose and the volume of lung in the radiation field, fractionation and younger age at therapy are risk factors for toxicity. Radiation can inflict damage directly to the lung tissue, and at higher doses, inhibit chest wall growth. This leads to diminished lung volumes and ultimately to restrictive lung disease, particularly when patients are young children at the time of therapy. In the Childhood Cancer Survivor Study, Mertens reported that survivors

exposed to chest radiation have a five-fold increased risk of abnormal chest wall development (RR=5.0; 95 % CI, 2.7–9.4), an over four-fold excess risk of lung fibrosis (RR=4.3; 95 % CI, 2.9–6.6) and an over twofold risk of chronic pneumonia (RR=2.2; 95 % CI, 1.5–7.0) [4].

Symptomatic radiation pneumonitis is a risk factor for long-term lung dysfunction as the acute changes associated with this condition often evolve to pulmonary fibrosis. Acute pneumonitis is usually only observed in patients who receive higher radiation doses (>30 Gy) to a significant portion of their lungs and is an uncommon outcome with contemporary therapy [6]. In these high doses, radiation toxicity is characterized by acute radiation pneumonitis, occurring within 1–3 months after radiation. Cough, pink sputum, dyspnea and pleuritis are common complaints during this subacute pneumonitis phase. When pulmonary-toxic chemotherapy (i.e., busulfan or melphalan) is combined with total body irradiation (e.g., for stem cell transplantation conditioning), reactions can occur during treatment. As mentioned, the acute changes of radiation pneumonitis may result in the development of pulmonary fibrosis. This fibrotic phase of injury can start within 3–6 months of post radiation completion, stabilizes after 1–2 years but can present clinically years following treatment. When symptomatic, pulmonary fibrosis usually presents with exertional dyspnea as well as chronic, non-productive cough. These clinical changes may be progressive, static or resolve over time. However, it is important to note, *the majority of chest RT survivors are clinically asymptomatic*. And yet while asymptomatic, many of these survivors may demonstrate sub-clinical radiographic and pulmonary function testing abnormalities, including diffusion capacity or abnormal restrictive or obstructive patterns that are common even after lower radiation doses [7].

The tolerance of the whole lung to fractionated RT doses is well described, especially in Wilms tumor survivors. Early studies on the outcomes of metastatic Wilms tumor survivors have shown that whole lung irradiation mainly affects the lung parenchyma and results in reduced lung volume, impaired lung compliance and hypoplasia and deformity of both the lung and chest wall [8–10]. In a series of metastatic Wilms tumor survivors

treated with whole lung irradiation (15 Gy in 10–14 daily fractions) combined with actinomycin, survivors had small lung volumes but normal gas transfer per unit lung volume when compared to predicted age and height reference ranges, suggesting that while lung RT results in chest wall underdevelopment, diffuse lung fibrosis is not significant at this dose level.

Studies in Wilms survivors have also demonstrated that exposure to partial lung radiation increase the risk for pulmonary late effects. Shaw and colleagues showed that Wilms survivors who had received partial lung radiation (20 Gy in 10 daily fractions) demonstrated significantly lower lung volumes than those who received no radiation. In addition, forced expiratory volume in 1 s (FEV1), residual volume, and total lung capacity were similar between those survivors who received whole lung radiation and those who received the partial lung radiation.

The majority of studies of pulmonary outcomes after chest radiation in lymphoma patients involve patients who were treated for Hodgkin lymphoma as adults [11–14]. The majority of these studies indicate asymptomatic restrictive lung disease in up to 30–40 % of those survivors exposed to chest radiation. Bossi and colleagues described the pulmonary outcomes of 27 pediatric Hodgkin lymphoma survivors and found that exposure to less than 20 Gy of mediastinal radiation was not associated with an increased risk of lung dysfunction. However, in patients who received over 20 Gy of mediastinal radiation and higher cumulative doses of bleomycin, pulmonary diffusion capacity was impaired [15]. In a Danish population-based study of the pulmonary function of survivors of pediatric Hodgkin lymphoma and non-Hodgkin lymphoma (N=41), Nysom and colleagues found that at a median of 11 years after diagnosis, total lung capacity and the diffusing capacity of the lung for carbon monoxide (DLCO) were reduced in both radiated and non-radiated patients who had received chemotherapy. Survivors who were treated with radiation at a young age were particularly at risk [16]. These findings have been confirmed in studies that demonstrated that combined treatment with chest radiation and bleomycin for Hodgkin lymphoma increases the risk of a persistent decrease in diffusion capacity [17, 18].

8.3 Chemotherapy-Associated Pulmonary Damage

Several chemotherapy agents can cause pulmonary dysfunction in long-term survivors. Antineoplastic drug-associated pulmonary damage may be the result of pneumonitis or fibrosis, hypersensitivity/allergy or idiosyncratic reactions. A dose–response toxicity has been demonstrated after treatment with bleomycin, chlorambucil or nitrosoureas. Damage mediated likely through an allergic effect, though very rare, is the result of methotrexate exposure.

Bleomycin, an antibiotic chemotherapy agent frequently used in Hodgkin lymphoma and germ cell tumor protocols, is the most common chemotherapy agent associated with lung injury in childhood cancer survivors. Bleomycin can cause acute pneumonitis as well as chronic lung toxicity. Toxicity is more common in older adults than in children. Pathophysiologic studies of bleomycin attribute its pulmonary injury to free radical formation and oxidative damage. Fibrosis develops post-treatment due to immune processes that include activation of effector cells, including alveolar macrophages, and release of cytokines, with tumor necrosis factor potentially playing a role. Usually, pulmonary abnormalities occur within 3–12 months after exposure and persist or progress.

Clinically, chronic toxicity or pulmonary fibrosis after bleomycin is characterized by impairment of gas diffusion between alveoli and pulmonary capillaries, and evidenced by a reduction in DLCO on pulmonary function testing. The greatest risk of bleomycin pulmonary toxicity has been observed with doses greater than 400 units/m^2, a dose seldom used in the treatment of pediatric patients. Although less common, pulmonary toxicity has been observed in children treated with 60–100 units/m^2. Bleomycin toxicity is variably exacerbated by concurrent or previous radiation treatment.

Alkylating agents, particularly the nitrosoureas, as well as cyclophosphamide, melphalan and busulfan have been implicated in late-onset lung fibrosis and chronic pulmonary dysfunction among childhood cancer survivors. Similar to those with symptomatic pulmonary disease associated with radiation therapy, pulmonary dysfunction due to chemotherapy exposure may include chronic cough or dyspnea associated with exercise intolerance.

The nitrosoureas (BCNU [carmustine] and CCNU [lomustine]) are alkylating agents that were used historically and commonly in the treatment of pediatric brain tumors. There is a clear relationship between cumulative dose of these agents and lung injury. When survivors are exposed to cumulative BCNU doses of more than 1,500 mg/m^2, more than 50 % will develop symptoms [19]. Lung injury may occur even at lower doses in individuals exposed to chest radiation. Long-term BCNU toxicity presents as pulmonary fibrosis. In a clinicopathologic study of 31 pediatric brain tumor patients exposed to BCNU 100 mg/m^2 every 6–8 weeks for up to 2 years, restrictive lung disease was reported after up to 17 years. Of the eight survivors alive at the time of study, four had clinical symptoms of shortness of breath and cough, six had signs of upper zone pulmonary fibrosis on chest X-ray and all eight had restrictive findings on pulmonary function testing [20].

Both cyclophosphamide and melphalan, in doses used for stem cell transplantation, have been implicated in late-onset pulmonary fibrosis, although the evidence for their toxicity is not as well established as with bleomycin and the nitrosoureas. Busulfan, generally when given at doses of more than 500 mg for stem cell transplant conditioning, causes toxicity and leads to a progressive restrictive lung disease pattern (defined as a decrease in forced vital capacity [FVC] and increase in FEV1/FVC in pulmonary function testing) [21]. As with other agents, concomitant exposure to chest radiation may exacerbate busulfan toxicity.

Other agents that occasionally cause lung injury include methotrexate, cytarabine and the vinca alkaloids. Both methotrexate and cytarabine have been associated with acute respiratory distress syndrome during treatment. Methotrexate has also been associated with hypersensitivity pneumonitis, chronic pneumonitis and fibrosis. This occurs at a frequency of less than 1 % and is thought to be an idiosyncratic hypersensitivity reaction to the drug. This toxicity is typically associated with rapid reversal and complete

recovery after drug withdrawal [22]. However, in a study of 26 pediatric leukemia survivors, 65 % of them had one or more abnormalities in vital capacity, total lung capacity, reserve volume or diffusion capacity [23]. Asymptomatic changes in pulmonary function tests that do not predict clinically significant problems have been associated with low dose oral administration for over 3 years, a treatment approach obsolete in pediatric cancer treatment. Case reports have linked vinblastine exposure to diffuse interstitial pulmonary infiltrates and chronic pulmonary changes.

Lastly, it is important to note that many chemotherapeutic agents, such as actinomycin D [24], bleomycin [25], cyclophosphamide [26], and doxorubin [27], potentiate the effects of radiation toxicity on the lung. Although doxorubicin is not pulmonary-toxic in itself, it magnifies the toxicity of the radiation [28]. In addition, toxicity to the lung is seen at much lower doses when pulmonary toxic drugs are combined than would be expected when given individually. For example, bleomycin in combination with other drugs such as cyclophosphamide, vincristine and doxorubicin magnify the risk for bleomycin-induced fibrosis [29].

8.4 Lung Injury After Stem Cell Transplantation

Hematopoietic stem cell transplant (HSCT) has become increasingly successful in curing pediatric patients of both solid and hematologic malignancies. Pulmonary complications are a major cause of post-transplant morbidity and mortality [30]. Pulmonary late effects following hematopoietic stem cell transplant are characterized by complex interactions between the conditioning regimen agents (i.e., total body irradiation, Busulfan, melphalan), non-infectious etiologies (i.e., pulmonary edema, bronchiolitis obliterans, bronchiolitis obliterans organizing pneumonia, diffuse alveolar hemorrhage, graft versus host disease), and infection during the period of hematopoietic and immune reconstitution (i.e., bacterial, fungal, cytomegalovirus [CMV], varicella zoster virus [VZV], and other viruses) [2] (see Fig. 8.1).

* BO=bronchiolitis obliterans; BOOP=bronchiolitis obliterans organizing pneumonia; DAH=diffuse alveolar hemorrhage; IPS=idiopathic pneumonia syndroma
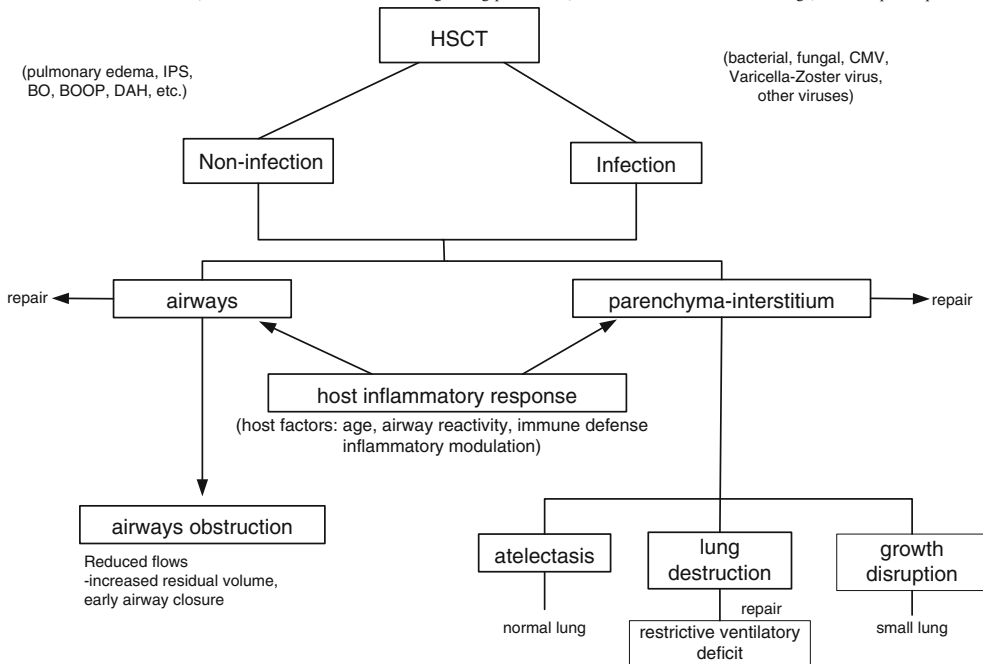

Fig. 8.1 Mechanisms of pulmonary dysfunction and/or growth by hematopoietic stem cell transplantation (HSCT). *BO* bronchiolitis obliterans, *BOOP* bronchiolitis obliterans organizing pneumonia, *DAH* diffuse alveolar hemorrhage, *IPS* idiopathic pneumonia syndroma

In other words, it is often difficult to discern which factors have the causative role in chronic lung disease. Both timing of the transplant and age at transplant are potential risk factors for late onset pulmonary morbidities. That is, those patients who received HSCT after two to three remissions (and therefore, most likely more chemotherapy incurring lung toxicity) had higher rates of these complications than those survivors transplanted in first remission [31]. Further, studies report that children transplanted at an older age had poorer pulmonary function testing values than those transplanted at a younger age [31]. Lastly, patients who have received prolonged immunosuppression for chronic graft versus host disease are at particular risk [31].

Patients undergoing total body irradiation as part of their conditioning regimen for stem cell transplantation have a high incidence of pulmonary late effects [21, 31]. As discussed, busulfan, carmustine, bleomycin and cyclophosphamide, all associated with pulmonary late sequelae, are known to cause pneumonitis and fibrosis after transplantation and this risk is increased in those who had previous radiation exposure or total-body irradiation for their preparative regimen.

Longitudinal data in survivors of HSCT during childhood demonstrate that there is a decline in lung volume and diffusing capacity from pre-transplant for 3–6 months post transplant, partial recovery for 1–2 years, and then stabilization for up to 10 years post transplant. The most common finding on pulmonary function testing is restrictive lung disease, sometimes associated with a decrease in DLCO [2]. In a cohort of 89 childhood cancer survivors post allogeneic HSCT, Inaba reported progressive worsening of pulmonary function as measured by forced mid-expiratory flow (25–50 %), residual volume, total lung capacity (TLC), and DLCO. Obstructive lung disease is also observed in HSCT survivors. For example, Bruno reported that in a series of 80 children treated with allogeneic HSCT, mean FEV1/FVC values of less than 60 % of predicted were observed in patients whose chronic graft versus host disease persisted 5 years after transplant.

8.5 Thoracic Surgery and Lung Damage

A mainstay of therapy for the treatment of pulmonary metastases (particularly metastatic osteosarcoma) is surgical resection. Although children are more adaptive to lung resection than adults, a study of adult childhood cancer survivors more than 30 years post resection, demonstrated increased rates of hypertrophy or hyperinflation of the remaining lung as a compensatory effect for the long-term loss in lung volume. Radiation exposure heightens the risk of pulmonary late effects when combined with surgical resection. In a Dutch cohort of childhood cancer survivors exposed to pulmonary toxic therapy, those with a history of surgical resection combined with radiation exposure had the highest increased risk of long-term pulmonary function impairment [5].

8.6 Other Risk Factors for Pulmonary Late Effects

In addition to therapeutic exposure, children with cancer may have other risk factors that predispose them to lung disease. These include underlying asthma or chronic obstructive lung disease, infection, cigarette or marijuana use, and exposure to environmental toxins. It is not known how the aging process and associated decline in lung function will affect survivors who had lung injury during cancer therapy in combination with other co-morbid heart or lung problems. This is an area prime for future research.

8.7 Detection, Screening and Management

Care of survivors at risk for pulmonary toxicity should include an annual medical history and physical examination, and careful review of a patient's treatment summary. Chest X-ray and pulmonary function testing (including DLCO and spirometry) are recommended at entry into a long-term follow-up program and then as clinically indicated in patients with abnormal results or clinical symptoms (see Table 8.1).

Table 8.1 Pulmonary late effects and guidelines for surveillance[a]

Exposure	Potential Late Effect(s)	Risk Factors	Greatest Risk Factors	Pulmonary Health Evaluation and Counseling
Bleomycin	Interstitial pneumonitis Pulmonary fibrosis ARDS (rare)	**Host Factors** Younger age at treatment **Treatment Factors** Higher cumulative dose Combined with: – Busulfan – BCNU – CCNU **Medical Conditions** Renal dysfunction High dose oxygen support such as during general anesthesia **Health Behaviors** Smoking	**Treatment Factors** Cumulative dose $\geq$400 U/m^2 (injury observed in doses 60–100 U/m^2)	**Evaluation** Yearly pulmonary exam **Screening** Chest X-ray (CXR) Pulmonary function tests (PFTs; including DLCO and spirometry) *Baseline at entry into long-term follow-up.* *Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.* **Counseling** Tobacco avoidance/smoking cessation To SCUBA dive, patients should have medical clearance from a pulmonologist For **Bleomycin** exposed survivors, notify healthcare providers of history of exposure and risk of worsening fibrosis with high dose oxygen exposure such as during general anesthesia.

Therapeutic Exposure	Potential Late Effects	Risk Factors	Highest Risk Factors	Other considerations
Alkylators – Busulfan – Carmustine (BCNU) – Lomustine (CCNU)	Pulmonary fibrosis	**Treatment Factors** Higher cumulative doses Combined with bleomycin **Medical Conditions** Atopic history **Health Behaviors** Smoking	**Treatment Factors** BCNU ≥600 mg/m² Busulfan ≥500 mg (transplant doses) Combined with: – Chest radiation – TBI	**Other considerations** In survivors with abnormal PFTs and/or CXR, consider repeat evaluation prior to general anesthesia Refer to pulmonologist in survivors with symptomatic or progressive pulmonary dysfunction. Yearly influenza vaccines. Appropriate pneumococcal vaccination.
Radiation – Chest – Whole lung – Mediastinum – Axilla – Mini-mantle – Extended mantle – Total Body Irradiation (TBI)	Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease – Growth abnormalities – Obstructive lung disease	**Host Factors** Younger age at irradiation **Treatment Factors** Radiation dose ≥10 Gy Chest radiation combined with TBI Radiation combined with: – Bleomycin – Busulfan – Carmustine (BCNU) – Lomustine (CCNU) – Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical Conditions** Atopic history **Health Behaviors** Smoking	**Treatment Factors** Radiation dose ≥15 Gy TBI ≥6 Gy in single fraction TBI ≥12 Gy fractionated	
Stem Cell Transplant – With any history of chronic GVHD	Bronchiolitis obliterans Chronic bronchitis Bronchiectasis	**Treatment Factors** Chest radiation TBI Pulmonary toxic chemotherapy: – Bleomycin – Busulfan – BCNU – CCNU	**Medical Conditions** Prolonged immunosuppression related to chronic graft versus host disease and its treatment	
Surgery – Pulmonary lobectomy – Pulmonary metastasectomy – Pulmonary wedge resection	Pulmonary dysfunction	**Treatment Factors** Combined with pulmonary toxic chemotherapy: – Bleomycin – Busulfan – BCNU – CCNU **Medical Conditions** Atopic History **Health Behaviors** Smoking	**Treatment Factors:** Combined with: – Chest radiation – TBI	

Table adapted from Children's Oncology Group Long-Term Follow Up Guidelines (www.survivorshipguidelines.org)

Pneumococcal and influenza vaccination should be considered. Smoking exacerbates the risk for lung dysfunction, and all at-risk survivors should be counseled regarding the importance of smoking avoidance or cessation. Anecdotal reports of progressive pulmonary fibrosis after exposure to high oxygen concentration (e.g., during anesthesia) has prompted the recommendation that survivors treated with bleomycin avoid exposure to concentrated oxygen and wear a MedicAlert bracelet documenting their risk. As such, for all bleomycin-exposed survivors and for all survivors with symptomatic pulmonary toxicity or abnormal PFTs after exposure to other pulmonary toxic therapy, an anesthesia consult should be obtained prior to any surgical procedures. SCUBA diving is controversial for long-term survivors and those with risk factors for pulmonary late effects should obtain medical clearance from a pulmonologist prior to diving. Finally, any survivors that demonstrate clinical signs or symptoms of pulmonary dysfunction or abnormal imaging or pulmonary function testing, should be considered for referral to a pulmonologist.

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