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Original Research

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Pulmonary Outcomes in Survivors of Childhood Cancer

A Systematic Review

Tseng-Tien Huang, PhD; Melissa M. Hudson, MD; Dennis C. Stokes, MD; Matthew J. Krasin, MD; Sheri L. Spunt, MD; and Kirsten K. Ness, PhD

Background: **The purpose of this article is to summarize the literature that documents the long-term impact of cancer treatment modalities on pulmonary function among survivors of cancer and to identify potential areas for further research.**

Methods: **Systematic reviews of clinical trials, observational studies, case series, and review articles were conducted. Articles were limited to the studies that discussed pulmonary toxicity or late effects among pediatric cancer survivors and to follow-up investigations that were conducted a minimum of 2 years after completion of cancer-related treatment or 1 year after hematopoietic stem cell transplant.**

Results: **Sixty publications (51 clinical studies/reports and nine reviews) published from January 1970 to June 2010 in PubMed met the inclusion criteria. Data showed an association between radiotherapy, alkylating agents, bleomycin, hematopoietic stem cell transplant, and thoracic surgery and pulmonary toxicity, as well as possible interactions among these modalities.**

Conclusions: **Pulmonary toxicity is a common long-term complication of exposure to certain anticancer therapies in childhood and can vary from subclinical to life threatening. Pulmonary function and associated loss of optimal exercise capacity may have adverse effects on long-term quality of life in survivors. Lung function diminishes as a function of normal aging, and the effects of early lung injury from cancer therapy may compound these changes. The information presented in this review is designed to provide a stimulus to promote both observational and interventional research that expands our knowledge and aids in the design of interventions to prevent or ameliorate pulmonary late effects among survivors of childhood cancer.** ***CHEST 2011; 140(4):881–901***

Abbreviations: ALL = acute lymphoblastic leukemia; BCNU = carmustine; CCNU = lomustine; DLCO = diffusing capacity of the lung for carbon monoxide; GVHD = graft-vs-host disease; gy = gray; HL = Hodgkin's lymphoma; HSCT = hematopoietic stem cell transplant; NHL = non-Hodgkin's lymphoma; PFT = pulmonary function testing; TLC = total lung capacity

Over the last 3 decades, therapeutic progress has resulted in a growing population of survivors of childhood cancer. In 2006, there were > 11 million cancer survivors in the United States, three times the number of survivors in 1971.[1] The 5-year survival rate for children diagnosed with cancer is approaching 85%,[2] and an estimated one in 570 individuals in the United States between the ages of 20 and 34 is a survivor of childhood cancer.[3]

Unfortunately, increased survival rates are not without consequences. There is substantial evidence

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Affiliations: From the Department of Epidemiology and Cancer Control (Drs Huang and Ness), the Department of Oncology (Drs Hudson and Spunt), the Department of Pediatric Pulmonary Medicine (Dr Stokes), and the Department of Radiological Sciences (Dr Krasin), St. Jude Children's Research Hospital, Memphis, TN.

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Correspondence to: Tseng-Tien Huang, PhD, Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Mail Stop 735, 262 Danny Thomas Place, Memphis, TN 38105; e-mail: tseng.huang@stjude.org

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that survivors of childhood cancer are at risk of developing various severe, disabling, or life-threatening conditions later in life.[4-6] Cancer treatment-related complications represent a major cause of morbidity that can have a profound effect on quality of life and can predispose to early mortality during adulthood. In a large-scale retrospective study of 5-year cancer survivors (N = 20,483), Armstrong et al[4] reported significant excess rates of death largely due to treatment-related causes rather than recurrence or progression of primary disease. Of note, pulmonary causes accounted for excess mortality risk (standard mortality ratio, 8.8), second only to deaths from subsequent cancers (standard mortality ratio, 15.2).[4] Chemotherapy and radiotherapy used to treat children with cancer can cause permanent lung damage.[7-9] The cumulative incidence of pulmonary complications increases with increasing time since diagnosis, suggesting that survivors of childhood cancer continue to face new-onset pulmonary morbidity as they age.[10]

This review provides a synopsis of current knowledge on the adverse effects on the lung of childhood cancer and its treatment. We summarize treatment modalities associated with pulmonary toxicity and review how these agents may interact and contribute to permanent lung dysfunction in adult survivors of childhood cancer. We also discuss other risk factors for pulmonary morbidity and mortality in this population, and identify knowledge deficits that should be addressed in future research to benefit the childhood cancer survivor population at risk of pulmonary late effects.

Materials and Methods

Criteria for Inclusion

We considered only the studies that discussed pulmonary toxicity or late effects among individuals with childhood-onset cancer and limited those to follow-up investigations that were conducted a minimum of 2 years after completion of cancer-related treatment or 1 year after hematopoietic stem cell transplant (HSCT). The primary outcome was defined as the occurrence of the pulmonary complications and a change in pulmonary function testing (PFT) results from serial evaluations.

Search Strategies

We searched the PubMed database (January 1970 to June 2010) for clinical trials, observational studies, case series, and reviews to include in our review. The key words "late effects" or "late sequelae" or "complications" AND "child" or "childhood" AND "cancer survivor" AND "lung" or "thorax" or "pulmonary" were combined with keywords for each therapeutic exposure. Accordingly, the keywords "radiation," "radiotherapy," or "ionizing radiation" were selected for radiation exposure; "chemotherapy" or "combined chemotherapy" for chemotherapy exposure; "stem cell transplant," "bone marrow transplant," "allogeneic" and/or "autologous bone marrow transplant" for HSCT; and "surgery," "resection," and/or "lobectomy" for surgery exposure. Reference lists of review articles and retrieved studies were also assessed for relevant titles.

Validity Assessment and Data Extraction

One author (T. H.) screened all retrieved reports and selected those that were potentially valid. To ascertain the validity of included studies, two authors independently assessed the selected studies for methologic quality.[11] Information was sought for the following four criteria: comparability of subject, clear definition of exposure or intervention, standard outcome measurement, and appropriate statistical analysis. The discrepancies of validity assessment were resolved by discussion. Of note, we were unable to use one of the Preferred Reporting Items for Systematic Review and MetaAnalysis commanded approaches, such as the Cochrane method for the assessment of risk of bias, because literature in this area includes many observational and few randomized studies. For each included study, patient characters, antitreatment exposure, follow-up period, sample size, and main study results were extracted.

Results

Search Results

The search of the PubMed database initially resulted in a total of 132 citations. After adjusting for duplicates, 130 remained. Of these, 76 studies were discarded because they did not meet the inclusion criteria (65 studies did not discuss pulmonary toxicity among childhood-onset cancer; eight studies investigated follow-up late effects no more than 2 years after completion; three studies investigated late effects among childhood cancer survivors within 1 year after HSCT). Another three papers were discarded because their full texts were not available. The reference lists of the remaining 51 studies were examined, and nine additional studies were identified that met the inclusion criteria. Thus, 60 publications (51 clinical studies/reports and nine reviews) from January 1970 to June 2010 were included in this review.

Description of Studies

Of 51 clinical studies, nine were prospective studies; the others were observational studies, except for one self-report study. No prior systematic review or meta-analysis on the adverse effects of childhood cancer and its treatment on the lung was identified. The treatment protocols varied by institution, classification, and timing of the primary diagnosis. The adverse effects of anticancer therapy on the lungs ranged from subclinical abnormalities on PFT to disabling and life-threatening pulmonary syndrome. The research demonstrated an association between radiotherapy, alkylating agents, bleomycin, HSCT, and thoracic surgery and pulmonary late effects among survivors of childhood cancer.

Study Quality and Risk of Bias

Table 1 provides an overview of study quality in the included publications. Overall, the included studies demonstrated a clear definition of exposure, valid outcome measure, and appropriate statistical analysis. Unfortunately, our ability to compare study populations was limited because many of the articles we located included single- or limited multi-institutional data derived from retrospective or cross-sectional investigations with samples of convenience. Additionally, the data presented from the earlier studies may not be relevant to current practice, because treatment of childhood cancer has changed substantially over time. Furthermore, because many studies were cross-sectional in nature, survivor bias may have excluded patients with more severe complications from PFT measurements at later time points. Nevertheless, this literature has value because the information helps define the extent and patterns of pulmonary dysfunction observed in adult survivors of childhood cancer, and offers clues about possible risk factors for long-term lung complications in this cohort.

Discussion

Summary of Evidence

Table 2 provides the summary of this systematic review. The results shows that certain therapeutic exposures, such as radiotherapy, specific alkylating agents, bleomycin, HSCT, and thoracic surgery, are linked to late pulmonary sequelae.

Disease- and Treatment-Induced Pulmonary Toxicity in Survivors of Childhood Cancer

Pulmonary dysfunction in survivors of childhood cancer results from primary or metastatic disease, antineoplastic therapy, and superimposed infections. Primary lung tumors are exceptionally rare in children.[63] However, the lung is a common site for metastases, even years following treatment.[64] Pulmonary toxicity as a result of anticancer therapy may range in severity from subclinical abnormalities on PFT to disabling and life-threatening pulmonary syndromes. Although pulmonary complications are essentially preventable by limiting the administration of offending drugs and irradiation, toxicity may be unavoidable if the toxic modalities are required to optimize tumor control.

Late Effects of Radiation in Survivors of Childhood Cancer: The late effects of radiation exposure are particularly important in children because both impaired organ development and skeletal growth defects may occur and magnify the problems related to lung injury. Self-reported data from 12,000 survivors in the Childhood Cancer Survivor Study showed that, compared with siblings, survivors treated with chest radiation had a fivefold increased risk of abnormal chest wall development (RR = 5; 95% CI, 2.7-9.4), a fourfold excess risk of developing lung fibrosis (RR = 4.3; 95% CI, 2.9-6.6), and a twofold excess risk of chronic pneumonia (RR = 2.2; 95% CI, 1.5-7.0).[39] In this cohort, the cumulative incidence of lung fibrosis was 3.5% within 20 years of diagnosis.

Table 3 lists the 22 reports published from January 1970 to June 2010 on radiation-induced pulmonary late effects among survivors of childhood cancer. Data from early studies on children treated for metastatic Wilms tumor demonstrate that irradiation of the thorax primarily affects the lung parenchyma and results in reduced lung volume,[13,14] impaired dynamic compliance,[14] and deformity of both the lung and chest wall.[12,14] The diffusing capacity of the lung for carbon monoxide (DLCO) may also be reduced.[12] In 1992, Attard-Montalto et al[20] described lung function in eight survivors of Wilms tumor (follow-up, 14.8 years) who had received whole-lung irradiation at 15.3 ± 1.8 gray (Gy) in 10 to 14 daily fractions, and actinomycin, a radiomimetic chemotherapeutic agent. These children demonstrated small lung volumes but normal gas transfer per unit lung volume (lung diffusion capacity corrected for alveolar ventilation) when compared with predicted values for age and height. This suggests that although pulmonary irradiation in childhood leads to underdevelopment of the thorax, diffuse lung fibrosis is unlikely to be a significant feature at this dose level.

Patients receiving partial-lung irradiation are also at risk of developing radiation-induced pulmonary late effects. In a cross-sectional study of 47 survivors of childhood Wilms tumor, Shaw et al[19] demonstrated that patients who had received partial-lung irradiation (20 Gy in 10 daily fractions) had significantly lower lung volumes than those who had received no irradiation. Lung diffusion capacity corrected for alveolar ventilation was significantly lower ($P < .05$) in the whole-lung radiation group (12 Gy in eight daily fractions) than the partial-lung irradiation group, but other PFT parameters, such as FEV_1, residual volume, and total lung capacity (TLC) were not significantly different between the two groups.

Although extensive data are available on lung function in adult survivors of Hodgkin's lymphoma (HL)/non-Hodgkin's lymphoma (NHL),[18,65-69] there are few studies on pulmonary function after childhood HL/NHL. Bossi et al[26] reported that children with HL who received mediastinal irradiation of > 20 Gy and higher cumulative doses of chemotherapy had a high risk of developing lung function abnormalities. Nysom et al[28] reported reduced TLC and DLCO in

Table 1—*Quality Measures of the Included Studies*

Study/Year	Trials Type	Comparability of Subject	Exposure or Intervention	Outcome Measurement	Statistical Analysis
Wohl et al[12]1975	Observational	No	Yes	Yes	Descriptive statistic only
Littman et al[13]/1976	Observational, prospective	No specific inclusion/ exclusion criteria	Yes	Yes	Yes
Benoist et al[14]/1982	Observational, prospective	No	Yes	Yes	Yes
Miller et al[15]/1986	Observational	Yes	No details of treatment exposure description	Yes	Yes
Shaw et al[16]/1989	Observational	Yes	No details of treatment exposure description	Yes	Yes
Mäkipernaa et al[17]/1989	Prospective	No	Yes	Yes	Descriptive statistic only
Shapiro et al[18]/1990	Observational	Yes	Yes, except short period of follow-up	Yes, using individual patients' pretherapy values to minimize variability	Yes
Shaw et al[19]/1991	Observational	Yes	Yes	Yes	Yes, except small sample size
Attard-Montalto et al[20]/1992	Observational	Yes	Yes	Yes	Descriptive statistic only; no reporting confounding variables
Hudson et al[21]/1993	RCT, prospective	Yes	Yes	Yes	Yes
Horning et al[22]/1994	Observational	Yes	Yes	Yes	Yes
Jakacki et al[23]/1995	Observational	Yes, but with adult participants	Yes	Yes	Yes
Jenny et al[24]/1995	Observational	Yes, but selection bias possible	Yes	Yes	Yes
Turner-Gomes et al[25]/1996	Cross-sectional	No	Yes	Yes	Yes
Bossi et al[26]/1997	Longitudinal	No	Yes	Yes	Yes
Nysom et al[27]/1998	Longitudinal	Yes	Yes	Yes	Yes
Nysom et al[28]/1998	Retrospective	Yes	Yes, except that several factors potentially impacting PFTs could not be distinguished	Yes	Yes
Saenz et al[29]/2000	Observational	No	Yes	Yes	Descriptive statistic only
Endicott et al[30]/2001	Retrospective	No	Yes	Yes	Descriptive statistic only
Laverdière et al[31]/2005	Retrospective	No	No clear outcome definition	NA	Yes
Weiner et al[32]/2006	Retrospective	No	Yes	Yes	Yes
Oguz et al[33]/2007	Cross-sectional	Yes	Yes	Yes	Yes, except no multiple comparison correctness
Mefferd et al[34]/1989	Observational	No	Yes	Yes	Descriptive statistic only
Marina et al[35]/1995	Observational	No	Yes	Yes	Yes and power calculation provided
Kaplan et al[36]/1996	Observational	No	Yes	Yes	Yes, except small size
Hale et al[37]/1999	Cross-sectional	Yes	Yes	Yes	Yes
O'Driscoll et al[38]/1990	Observational	Yes	Yes	Yes	Descriptive statistic only

(Continued)

Table 1—*Continued*

Study/Year	Trials Type	Comparability of Subject	Exposure or Intervention	Outcome Measurement	Statistical Analysis
Mertens et al[39]/2002	Retrospective self-report	Yes	Yes	Yes	Yes
Serota et al[40]/1984	Observational, prospective	No	Yes	Yes	Descriptive statistic only
Stokes[41]/1987	Retrospective	No	Yes	Yes	Descriptive statistic only
Uderzo et al[42]/1991	Observational	No	Yes	Yes	Descriptive statistic only
Arvidson et al[43]/1994	Prospective	No	Yes	Yes	Yes
Schultz et al[44]/1994	Retrospective	No	Yes	Yes	Yes
Kaplan et al[45]/1994	Retrospective	No	Yes	Yes	Yes
Rovelli et al[46]/1995	Longitudinal	Yes	Yes	Yes	Yes, except no multiple comparison correctness
Nenadov Beck et al[47]/1995	Cross-sectional	Yes	Yes	Yes	Yes
Nysom et al[48]/1996	Longitudinal	Yes	Yes	Yes	Yes
Fanfulla et al[49]/1997	Prospective	No	Yes	Yes	Yes
Nève et al[50]/1999	Prospective	Yes	Yes	Yes	Yes
Cerveri et al[51]/1999	Cross-sectional	Yes	Yes	Yes	Yes
Leneveu et al[52]/1999	Prospective	Yes	Yes	Yes	Yes
Griese et al[53]/2000	Retrospective	Yes	Yes	Yes	Yes
Cerveri et al[54]/2001	Prospective	Yes	Yes	Yes	Yes
Bruno et al[55]/2004	Retrospective	Yes	Yes	Yes	Yes
Frisk et al[56]/2004	Prospective	Yes	Yes	Yes	Yes, except small size
Faraci et al[57]/2005	Retrospective	No	Yes	Yes	Yes
Hoffmeister et al[58]/2006	Largest-cross sectional	Yes, but selection bias possible	Yes	Yes	Yes
Leung et al[59]/2007	Prospective	Yes	Yes	Yes	Yes
Efrati et al[60]/2008	Retrospective	No	Yes	Yes	Yes, except no multiple comparison correctness
Ricardi et al[61]/2009	Retrospective	No	Yes	Yes	Yes
Inaba et al[62]/2010	Longitudinal	No	Yes	Yes	Yes

NA = not available; PFT = pulmonary function testing; RCT = randomized controlled trial.

Table 2—*Treatment Exposures-Based Risk Factors for Development of Late Effects in Survivors of Childhood Cancer*

Treatment Exposures	Potential Late Effects	Risk Factors
Radiation	Pulmonary toxicity	Host factors
	Pulmonary fibrosis	Younger age at irradiation
	Interstitial pneumonitis	Treatment factors
	Restrictive lung disease	Radiation dose ≥ 15 Gy
	Obstructive lung disease	Chest radiation combined with TBI
		Radiation combined with
		Bleomycin
		BCNU
		CCNU
		Radiomimetic chemotherapy (eg, doxorubicin, dactinomycin)
		Medical conditions
		Atopic history
		Health behaviors
		Smoking
Alkylating agents:	Pulmonary fibrosis	Treatment factors
Busulfan		Higher cumulative doses (>500 mg) combined with radiation
BCNU		Medical conditions
		Atopic history
CCNU		Health behavior
		Smoking
Bleomycin	Pulmonary toxicity	Host factors
	Interstitial pneumonitis	Younger age at treatment
	Pulmonary fibrosis	Treatment factors
	ARDS (very rare)	Higher cumulative doses (≥ 400 units/m^2) combined with
		Chest irradiation
		Busulfan
		BCNU
		CCNU
		Medical conditions
		Renal dysfunction
		High-dose oxygen support such as during general anesthesia
		Health behavior
		Smoking
HSCT with any history of chronic GVHD	Pulmonary toxicity	Host factors
	BO	Younger age at HSCT
	BOOP	Treatment factors
	IPS	Chest radiation
	Restrictive lung disease	TBI
	Obstructive lung disease	High-dose chemotherapy
		Pulmonary toxic chemotherapy
		Bleomycin
		Busulfan
		BCNU
		CCNU
Surgery	Pulmonary dysfunction	Treatment factors
Pulmonary lobectomy		Combined with pulmonary toxicity therapy
Pulmonary metastasectomy		Bleomycin
Pulmonary wedge resection		Busulfan
		BCNU
		CCNU
		Medical conditions
		Atopic history
		Health behaviors
		Smoking

BCNU = carmustine; BO = bronchiolitis obliterans; BOOP = bronchiolitis obliterans organizing pneumonia; CCNU = lomustine; GVHD = graft-vs-host disease; Gy = gray; HSCT = hematopoietic stem cell transplant; IPS = idiopathic pneumonia syndrome; TBI = total body irradiation.

41 children treated for malignant lymphoma with chemotherapy with or without radiation. Oguz et al[33] reported reduced lung volumes and DLCO among 13% (10 of 77) of survivors of childhood HL/NHL at a median 5 years post diagnosis.

Pulmonary Function and Loss of Optimal Exercise Capacity: Mild restrictive lung disease has also been reported as a potential outcome after treatment of childhood-onset acute lymphoblastic leukemia (ALL), and may eventually lead to reduced exercise capacity.

Table 3—*Radiation-Induced Pulmonary Late Sequelae in Long-term Survivors of Childhood Cancer*

Study	No. of Patients	Age at Diagnosis, y, median	Diagnosis	Follow-up, y, median	Chemotherapy Agents	RT	RT Dose	Late Effects
Wohl et al[12]	20	0.5-4.4 (2.7)[a]	Wilms tumor	6.8-17.1 (11.4)[a]	Actinomycin D	WLR	10.2 Gy (SD 1.4) in 6 pts (group 1); 23.7 Gy (SD 11.2) in 6 pts (group 2)	100% (12 pts) abnormal in TLC/DLCO with WLR (mean TLC 71% predicted value in group 1 and mean TLC 58% predicted value in group 2)
Littman et al[13]	33	0.4-10 (3.5)	Wilms tumor	4-20 (6)	Actinomycin D	WLR	11.6-13.7 Gy in 15 pts	Moderately reduced lung volumes in the radiated group
Benoist et al[14]	48	1-12 (3.8)[a]	Wilms tumor	2-17 (7.3)[a]	Actinomycin D	WLR	20 Gy	Reduced lung volumes/thoracic diameters and deformity of the lower thoracic spine; DLCO normal
Miller et al[15]	29	1-9 (3.7)[a]	Leukemia (n = 15) and solid tumors (n = 14)	4-13 (8.2)[a]	Cyclophosphamide	Thoracic	15-60 Gy in 5 pts	80% (n = 4) of those receiving thoracic radiation had abnormal PFT (FVC and TLC); 38% (n = 9) who did not receive thoracic radiation had abnormal PFT; DLCO and FEV_1 normal
Shaw et al[16]	38	2-11.8 (5.6)[a]	ALL	2.3-20 (9.8)[a]	Cyclophosphamide	TBI/SP	TBI/SP in 5 pts	Of 26 pts with complete data, 65% (n = 17) had abnormal PFT
Mäkipernaa et al[17]	40	0.02-17.5 (4.5)	Solid tumors	11-27 (17.5)	Cyclophosphamide, vincristine, actinomycin D, doxorubicin, procarbazine, nitrogen mustard	Chest	17.7-64.5 Gy in 21 pts	43% (n = 17) had a chest deformity; 20% (n = 8) had evidence of fibrosis; 48% (n = 19) abnormal PFT; 8% (n = 3) abnormal DLCO.
Shapiro et al[18]	13[b]	14-66 (29.4)[a]	HD	2.2-7.6 (4.6)		Thoracic	26-47 Gy	62% (n = 8) had an apical fibrosis or pleural thickening; no respiratory symptoms attributed to therapy were noted
Shaw et al[19]	4[c]	WLR group, 3.7-9.3 (7); involved region group: 1.3-10 (4.4); nonradiation group: 0.7-10.3 (3.0)	Wilms tumor	3.5 in WLR group; 8.2 in involved region group; 3.5 in nonradiation group[d]	Cyclophosphamide, act inomycin D, doxorubicin	Involved region/ WLR	Involved region in 17 pts (20 Gy); WLR in 3 pts (12 Gy)	Patients receiving WLR had lower DLCO than those in nonradiation group; PFT values were lower in the involved region group than the nonradiation group
Attard-Montalto et al[20]	8	3-11.2 (5.7)[a]	Wilms tumor	6-27 (14.8)[a]	Cyclophosphamide, actinomycin D, doxorubicin, vincristine	WLR	15.3 Gy (SD 1.8)	75% (n = 6) abnormal in FEV_1 (mean FEV_1: 67% predicted value) 0.63% (n = 5) abnormal in DLCO; all patients had reduced lung volumes; 3 were asymptomatic

(Continued)

Table 3—*Continued*

Study	No. of Patients	Age at Diagnosis, y, median	Diagnosis	Follow-up, y, median	Chemotherapy Agents	RT	RT Dose	Late Effects
Hudson et al[21]	85	4-20 (14)	HD	0.3-9 (3.8)	COP, ABVD	Involved region	20 Gy	58% (n = 45) had abnormal radiograph findings; 22% (n = 19) had abnormal PFT; < 1% (n = 1) had a fibrosis
Horning et al[22]	145	13-58 (26)	HD	Two time periods: (1) within 1.3 y and (2) > 3 y	ABVD/MOPP	Mantle	44 Gy	Patients with mantle radiation had a more pronounced reduction in FVC and DLCO and less complete recovery than those who did not receive mantle radiation
Jakacki et al[23]	28	3.9-36.7 (11.4)	Malignant brain tumor	0.5-11.6 (2.6)	CCNU	SP	36 Gy with a 18-36 Gy boost	50% (n = 14) abnormal in PFT (RLD pattern); 50% (n = 35) had chest infections; reduced lung volumes and exercise intolerance were seen (≈20 pts had < 80% predicted of FVC, RV, DLCO, TLC, and FEV_1)
Jenney et al[24]	70	1.5-15 (5.8)	Leukemia	0.6-18.5 (4.2)	Cyclophosphamide, doxorubicin	TBI/SP	TBI in 14 pts (7-14 Gy), SP in 55 pts (18-24 Gy)	
Turner-Gomes et al[25]	19	1.5-17.7 (4.6)	ALL	1.1-7.1 (4.6)[a]	Doxorubicin	…	…	All were asymptomatic; PFT were within normal limits in all patients
Bossi et al[26]	27	2-16 (11)	HD	0.3-13 (7)	MOPP/ABVD	Mantle	25.4 Gy (SD 6) in 19 pts	18% had an abnormal FVC score; 40% an abnormal DLCO score; 3 pts were symptomatic; oxygen saturation was normal in all pts
Nysom et al[27]	94	0.5-14.8 (3.9)	ALL (patients had never been treated with HSCT or SP)	1-18 (8)	Cyclophosphamide, anthracyclines, vincristine/ prednisone	CNS prophylaxis	15-18 Gy in 23 pts, 24 Gy in 16 pts	39% (n = 37) abnormal in PFT: 25 pts had a restrictive pattern, 10 pts had reduced DLCO score, and 2 pts had an obstructive pattern; 10 were symptomatic
Nysom et al[28]	41	3.9-15 (11)	HD (n = 22) and NHL (n = 19)	2.3-23.7 (10.5)	Bleomycin, BCNU, cyclophosphamide, doxorubicin, methotrexate, procarbazine	Mantle/CNS prophylaxis	Mantle in 21 pts (37-40 Gy), CNS in 6 pts (24 Gy)	On average, TLC was reduced to −0.9 standardized residual and DLCO was reduced to −1.3 standardized residual; 27% (n = 11) abnormal in PFT; 39% (n = 16) abnormal in DLCO
Saenz et al[29]	20	2.5-21 (13)	Chest wall tumors undergoing surgical resection	0.58-19.4 (3.0)	Varied, mainly on vincristine, doxorubicin, cyclophosphamide	External beam, intraoperative RT, brachytherapy	30 Gy in 10 pts (external beam); 12 Gy in 4 pts (intraoperative RT); 40 Gy in 1 pt (brachytherapy); none in 5 pts	There was no surgical mortality, but only 11/20 were alive after the follow-up; 2 died of pulmonary embolus and pneumothorax

(Continued)

Table 3—*Continued*

Study	No. of Patients	Age at Diagnosis, y, median	Diagnosis	Follow-up, y, median	Chemotherapy Agents	RT	RT Dose	Late Effects
Endicott et al[30]	21	3.3-41.6 (7.5)[e]	Malignant brain tumor	3.2-27.2 (10.7)	CCNU	SP	35 Gy (SD 4.3)	43% (n = 9) abnormal in PFT (5 with restrictive changes, one with reduced DLCO, and 3 with obstructive disease); these changes were mild and patients were predominantly asymptomatic
Laverdière et al[31]	53	3	Advanced-stage neuroblastoma	1.9-25.5 (7.06)	Cyclophosphamide, doxorubicin, cisplatin, etoposide, carboplatin	Abdominal, chest, cranial, spinal, TBI	22 Gy in abdomen of 46 pts; 20 Gy in chest of 15 pts; 24 Gy in cranium of 15 pts; 21 Gy in spine of 6 pts; 11 Gy in TBI of 6 pts	Restrictive lung pattern:10; obstructive lung pattern: 2; the survivors who received radiation to chest area had a higher risk of developing pulmonary dysfunction compared with the survivors who did not receive chest radiation (OR, 7.3; 95% CI, 1.6-32.9; $P = .009$)
Weiner et al[32]	30	1.8-18 (7.6)	Wilms tumor (n = 15), HD (n = 3), sarcoma (n = 11), and hepatoblastoma (n = 1)	0-13.7 (2.8)	Doxorubicin, bleomycin	WLR	12 Gy	Ten had self-reported pulmonary symptoms; 50% had abnormal FEV_1; 17% of pts had mild reduction in TLC, whereas 13% had minor and 30% had severe reductions; 38% had mild reduction in DLCO, whereas 29% had moderate and 14% had severe reductions
Oguz et al[33]	75	1.8-15 (8)	HD (n = 37), NHL (n = 38)	2-13 (5)	COP/ABVD	Thoracic	Thoracic radiation (24 Gy) in 23 pts	All were asymptomatic, 23% (n = 17) had interstitial fibroses, 13% (n = 10) abnormal PFT. There were no significant differences in PFT parameters between pts with HD and those with NHL

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; ALL = acute lymphoblastic leukemia; COP = cyclophosphamide, vincristine, and procarbazine; DLCO = diffusing capacity for carbon monoxide; HD = Hodgkin's disease; MOPP = mechlorethamine, vincristine, procarbazine, and prednisone; NHL = non-Hodgkin's lymphoma; pt = patient; RLD = restrictive lung disease; RT = radiotherapy; RV = residual volume; SP = spinal radiation; TLC = total lung capacity; WLR = whole lung radiation. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Data reported as y (mean).

[b]Two children and 11 adults.

[c]Three in WLR group, 17 in involved region group, and 23 in nonradiation group.

[d]Median(s).

[e]Reported as age at radiotherapy.

In a cohort study of 38 survivors of childhood-onset ALL, >50% had one or more abnormalities in PFTs.[26] Similar data were reported in another study on a mixed cohort (15 ALL and 14 solid-tumor survivors), in which 48% had pulmonary function abnormalities.[15] In a study by Jenney et al[24] of lung function and exercise capacity in 70 survivors of childhood leukemia at a median of 6 years after diagnosis, >50% of survivors had lower lung volumes and impaired maximal exercise capacity with a reduction of maximal workload, maximal oxygen uptake, and maximal ventilation than normal controls. Exercise performance at submaximal levels was also affected. Of note, one-half of the subjects who participated in the study had chest infection during, or subsequent to, their treatment of leukemia. It is known that children who undergo acute respiratory insult may develop more chronic problems as they age.[70] This was confirmed in a multivariate analysis,[24] in which chest infection occurring during treatment was identified as a risk factor for reduced lung volumes as well as transfer factor. Other risk factors identified for reduced lung volumes in childhood leukemia were cyclophosphamide and craniospinal irradiation, whereas reduced transfer factors were doxorubicin, craniospinal irradiation, and HSCT.

Chemotherapy-Induced Injury

Previous investigations that have documented that pulmonary function is compromised by exposure to specific chemotherapeutic agents, including bleomycin, carmustine (BCNU), lomustine (CCNU), busulfan, and cyclophosphamide are summarized in Table 4.

Bleomycin-Induced Pulmonary Toxicities: Several distinct pulmonary syndromes are associated with bleomycin exposure, including bronchiolitis obliterans organizing pneumonia (BOOP), eosinophilic hypersensitivity, and, most commonly, interstitial pneumonia, which may ultimately progress to fibrosis.[71] The onset of pulmonary fibrosis generally occurs several months after completion of therapy. At present, the pathogenesis of bleomycin-induced pulmonary toxicity is not well understood. However, bleomycin is poorly metabolized in the lung because this organ has low levels of the bleomycin-detoxifying enzyme, bleomycin hydrolase.[72] Bleomycin accumulation damages endothelial cells in lung vasculature, resulting in accumulation of inflammatory cells (macrophages, lymphocytes, and neutrophils) and fibroblasts in the lung parenchyma.[71-73] The effects of bleomycin can be harmful and even potentially fatal.[73] Research shows that bleomycin at total cumulative doses of 400 units is associated with the development of fibrosis in 10% of adult patients without other risk factors, and a death rate of 1% to 2% among those patients. Below this threshold, the incidence of pulmonary toxicity is estimated to be between 3% and 5%.[74]

Little has been written on bleomycin toxicity in childhood cancer survivors. In a study by Hale et al,[37] PFTs in 13 children treated for germ cell tumors with bleomycin (median dosage, 120 mg/m^2) revealed pulmonary dysfunction in eight patients. Mefferd et al[34] demonstrated pulmonary dysfunction by exposure to bleomycin (a maximum dose of 60 units/m^2) among surviving children with HL.

Concomitant or subsequent thoracic irradiation, administration of other chemotherapeutic agents, and/or oxygen therapy may exacerbate bleomycin-induced lung injury. A review of published clinical studies[75,76] and a randomized trial[77] indicate that the incidence of pulmonary fibrosis rises when bleomycin and radiotherapy are used together. Cyclophosphamide, vincristine, doxorubicin, and methotrexate with bleomycin have also been reported to increase the risk of fibrosis.[7]

Goldiner et al[78] reported that the use of oxygen therapy (mean concentration, 39%) during and after pulmonary resection in five patients with testicular cancer who were treated with bleomycin (400 ± 180 mg) 6 to 12 months prior, resulted in 100% mortality because of respiratory distress. Postmortem examination showed severe alveolar wall damage consistent with bleomycin-induced pulmonary injury. In a subsequent study by Goldiner and Schweizer,[79] 12 patients with similar medical profiles maintained on an oxygen concentration of ≤25% had no respiratory complications. Ingrassia et al[80] also reported that patients who had previously received bleomycin and then needed oxygen support during surgery were susceptible to the development of lung toxicity. Because activated bleomycin induces its toxicity in part by the production of free radicals, the administration of a high dose of inspired oxygen likely magnifies the risk of toxicity.

Alkylating Agents and Lung Dysfunction: In children, busulfan may be used as part of the conditioning regimen for HSCT. Busulfan-induced toxicity usually develops insidiously. Symptoms include a nonproductive cough, dyspnea, or fever. The average time from initiation of therapy to onset of respiratory symptoms is 3.5 years (range, 8 months to 10 years).[81] It is unclear whether busulfan-related injury is dose dependent, but there are no reports of lung injury in patients receiving doses of busulfan of <500 mg in the absence of other toxic agents.[82] As with other chemotherapeutic agents, concomitant irradiation may magnify the effect of busulfan. The chest radiograph in patients with busulfan toxicity reveals a

Table 4—*Studies of Pulmonary Sequelae After Bleomycin or Alkylating Agents Among Surviving Children*

Study	Patient Population	Age at Diagnosis, y	Follow-up	Treatment	Late Effects
Mefferd et al[34]	20 asymptomatic surviving children with Hodgkin's lymphoma	5-17	27.5 mo	All received combined modality therapy of 6 cycles of alternating ABVD/MOPP chemotherapy and low-dose (15-25 Gy) involved field RT	6/20 pts showed restrictive pattern and 2/20 had obstructive dysfunction; these abnormalities were observed following a maximum bleomycin dose of 60 units/m^2
Marina et al[35]	37 pts treated for Hodgkin's lymphoma who had adequate serial PFTs	15 (6-20)	93 mo (56-126 mo)	COP/ABVD chemotherapy and low-dose (14-20 Gy) mantle radiation The median delivered bleomycin cumulative dose: 60 mg/m^2 (20-100 mg/m^2)	At 2 y post diagnosis, DLCO/VA remained significantly decreased compared with that value at diagnosis period
Kaplan et al[36]	17 pts treated for rhabdomyosarcoma	10.1 ± 7.2 (0.01-23.5)	7 y (2.2-14.4 y)	Surgery, radiation, and multiple drug regimens (dactinomycin, cyclophosphamide, doxorubicin, vincristine, bleomycin, and methotrexate)	≈87% of study pts had a lower TLC value; 70% of study pts had a lower DLCO value than the normal limits
Hale et al[37]	Of 73 pts treated for extracranial germ cell tumors, 18 had received bleomycin (median cumulative dosage, 120 mg/m^2)	Median age at diagnosis 9.2	11.3 y (5.1-26.5 y)	Of 73 pts, surgery alone (n = 17); RT + surgery (n = 8); RT + chemotherapy + surgery (n = 21); chemotherapy + surgery (n = 27)	13/18 pts who received bleomycin revealed restrictive (n = 5) or diffusion (n = 3) abnormalities, but only 3 of these pts were clinically symptomatic
O'Driscoll et al[38]	31 children with malignant brain tumor (14 had died of their primary tumor)	1-16 (median 7.5)	8-17 y (median 14 y)	Underwent surgery and had RT to the cranium or craniospinal axis; total carmustine dose: 1,270 (770-1,800) mg/m^2	35% (n = 6) died of lung fibrosis; all pts with complete data (n = 8) had abnormal PFT
Mertens et al[39] (self-report study)	Childhood Cancer Survivors Study cohort (12,390 childhood cancer survivors and 3,546 randomly selected siblings)	0-20	Survival for ≥ 5 y from the time of diagnosis	Multivariate analyses were used to determine the relative risks with 95% CIs of reported pulmonary conditions by exposure to the following treatment variables: bleomycin, cyclophosphamide, busulfan, CCNU, and/or BCNU	Significant associations were present for supplemental oxygen use and BCNU (RR, 1.4), bleomycin (RR, 1.7), busulfan (RR, 3.2), CCNU (RR, 2.1), and cyclophosphamide (RR, 1.5); for recurrent pneumonia and cyclophosphamide (RR, 1.6); for chronic cough and bleomycin (RR, 1.9) and cyclophosphamide (RR, 1.3); and for pleurisy and busulfan (RR, 5.1)

DLCO/VA = diffusing capacity of the lung for carbon monoxide per unit of alveolar volume; RR = rate ratio. See Table 1 to 3 legends for expansion of other abbreviations.

combined alveolar and interstitial infiltrative pattern. Pathologic findings include lymphocytic and plasma cell interstitial infiltration, type 2 hyperplasia, and interstitial fibrosis that are more severe than those seen in other chemotherapy-induced pulmonary toxicities.[81,83]

Cyclophosphamide is an alkylating agent used to treat hematologic and solid-tumor malignancies, in HSCT preparative regimens, and as an immunosuppressant for nonmalignant disorders. Clinical features of cyclophosphamide-induced lung toxicity include dyspnea, fever, cough, gas exchange abnormalities on PFTs, parenchymal infiltrates, and pleural thickening.[84] Two distinct patterns of cyclophosphamide-induced lung toxicity have been identified.[84] Early-onset pneumonitis may appear up to 6 months after exposure but resolves with drug withdrawal or corticosteroid administration. Late-onset pneumonitis appears more than 6 months after exposure and does not respond to cessation of cyclophosphamide and/or corticosteroid administration. Late-onset disease is rare ($<1\%$ of those exposed), but often progresses to fibrosis.[85] There is no apparent relationship between the development of lung injury and the dose of cyclophosphamide or duration of its use.[81,82,86]

Nitrosoureas are a class of agents with both alkylating and carbamylating activities. They are widely used to treat gliomas and other CNS tumors, and are also included in conditioning for autologous HSCT.[81] There is a clear relationship between nitrosoureas cumulative dose and lung injury; and long-term injury may be present even without acute evidence of injury. BCNU-induced lung injury occurs in 20% to 30% of treated patients overall,[76] and increases to 50% in patients who receive a total dose of $>1{,}500$ mg/m^2.[87] Lung injury may even occur at lower doses in individuals who have previously received thoracic radiation.[86] Symptoms such as dyspnea, tachypnea, and nonproductive cough, may develop as early as 1 month after initiation of therapy.[88]

Long-term BCNU toxicity appears as fibrosis. It is insidious in onset, follows a bibasilar reticular pattern,[88] and seems to be intractably progressive. Corticosteroid therapy is ineffective.[81] In a review of 17 survivors of childhood brain tumor, restrictive changes with lung fibrosis were reported as long as 25 years after exposure to BCNU at 100 mg/m^2 every 6 to 8 weeks for 2 years.[38] Nine of 17 survivors died of pulmonary fibrosis, two within 3 years of treatment, four within 6 and 13 years of treatment, and three within 13 to 25 years of treatment. Of the eight patients still alive 25 years after treatment, follow-up data from seven survivors showed evidence of upper zone pulmonary fibrosis.[89]

Lung fibrosis has also been associated with similar agents, such as CCNU and methyl-CCNU (semustine), but appears to be less common.[88] Clinical and histologic findings are similar to those seen for pulmonary toxicity caused by BCNU.

Other Chemotherapy Agents: Methotrexate, teniposide (VM-26), and cytarabine have been associated with noncardiogenic pulmonary edema, a rare acute complication of therapy.[83] Signs and symptoms are no different from those of noncardiogenic pulmonary edema associated with other causes.[83] Methotrexate-induced pulmonary toxicity may manifest as hypersensitivity pneumonitis, which is typically associated with rapid reversal and complete recovery after drug withdrawal.[86,88]

The taxanes are a group of new-generation anticancer agents used broadly in adult cancer protocols. Their use is evolving in pediatric cancer protocols.[90] These agents are associated with pulmonary toxicity in adults, usually manifested as nonspecific interstitial pneumonitis, diffuse alveolar damage, and pleural effusion.[91] Gemcitabine has also been recognized to induce pulmonary toxicity, in about 10% of patients.[92] Gemcitabine-induced pneumonitis is likely a cytokine-mediated inflammatory reaction of the alveolar capillary wall. It appears as noncardiogenic pulmonary edema, diffuse alveolar damage, or alveolar hemorrhage.[93]

HSCT and Lung Injury

HSCT is now an established treatment approach for many malignant and nonmalignant diseases. Pulmonary complications are a major cause of posttransplant morbidity and mortality.[94] In a retrospective review of 363 children undergoing HSCT over a 5-year period, Eikenberry et al[95] reported that those with pulmonary complications had higher mortality rates than those who did not (65% vs 44%, $P<.01$). Pulmonary complications among HSCT patients are heterogeneous in their frequency, timing, and outcomes.[96] Complications are related to either the transplant process or the transplant preparative regimen, and are divided into four main categories: (1) conditioning regimen toxicity; (2) infectious complications, which occur during the period of hematopoietic and immune reconstitution; (3) noninfectious complications, which occur because of the chemotherapy or radiotherapy used in the conditioning regimen; and (4) complications due to alloreactivity, which occur after allogeneic transplant.

Late Effects of HSCT in Survivors of Childhood Cancer: Table 5 lists the 23 studies of late sequelae after HSCT published from January 1970 to June 2010 among children transplanted primarily for malignancies. Late sequelae after HSCT are characterized

by complex interactions between the infectious/noninfectious agents and the lung (Fig 1). Infectious agents are an important source of complications following HSCT in children. Children remain at risk of bacterial and fungal infections if they develop graft-vs-host disease (GVHD) and are also at risk of viral infection, particularly reactivation of herpes viruses such as cytomegalovirus.[97] Ferry et al[98] reported that the 10-year cumulative incidence of first episode of infection in 112 children was 31% ± 4% and in nine patients it involved the pulmonary system (gram-negative infection of respiratory tract, n = 5; viral influenza with lung extension, n = 2; pulmonary aspergillosis, n = 1; and pneumocystis carinii, n = 1).

Longitudinal HSCT data in children show that there is a decline in lung volume and diffusing capacity from pretransplant for 3 to 6 months post transplant, partial recovery for 1 to 2 years, and then stabilization for up to 10 years post transplant.[43,45,46,48,49,52,55,99] The most commonly reported finding is a restrictive ventilatory deficit, sometimes associated with a decrease in DLCO.[40,42,43,45,47-49,50,51,53-55,58] In a cohort of survivors of childhood hematologic malignancies after allogeneic HSCT (n = 89), Inaba et al[62] showed progressive worsening of pulmonary function measured with forced midexpiratory flow (25%-75%), residual volume, TLC, and DLCO during a median follow-up of 8.9 years.

Obstructive disease associated with chronic GVHD can also occur among children who received HSCT.[44,55] In a retrospective study of 80 children treated with allogeneic HSCT during a 16-year period, Bruno et al[55] reported mean FEV_1/FVC values of < 60% predicted for patients whose chronic GVHD persisted 5 years post HSCT. In a large cross-sectional study, Hoffmeister et al[58] examined the prevalence of pulmonary dysfunction in survivors of pediatric HSCT, 175 of whom were transplanted for hematologic malignancies and 40 for nonmalignant diseases (median transplant age, 8.3 years; range, 0.3-18.0 years). PFTs performed 10 years post HSCT showed that 40% of patients had either restrictive lung deficits or obstructive lung disease.

Both the timing of the transplant and the age at transplant have been indicated as potential risk factors for the development of late-onset pulmonary abnormalities. In a cross-sectional study of 52 children with hematologic malignancies, Cerveri et al[51] reported that the percentage of patients with pulmonary abnormalities was higher in patients who received HSCT after two or three complete remissions than in those who were transplanted immediately after the first remission (54% vs 21%; $P < .02$). This is not surprising given that many first-line chemotherapeutic agents such as cyclophosphamide, methotrexate, and cytosine arabinoside have been reported to cause lung toxicity. Quigley et al[99] reported a trend toward worsening PFTs with increasing age in 25 children receiving HSCT for different neoplastic malignancies. Arvidson et al[43] and Leneveu et al[52] reported that children transplanted at a young age had better PFT values than those transplanted at an older age.

Thoracic Surgery and Lung Damage

Surgical resection remains a key component of the treatment of pulmonary metastasis in children.[100] Children appear to tolerate resection better than do adults.[101,102] In one study, among adults who were treated for childhood cancer and who were ≥ 30 years post pulmonary resection, adaptive mechanisms, such as hypertrophy or hyperinflation of the remaining lungs, were present to compensate for the loss in lung tissue in the long term.[103]

Interactions

Chemotherapy-Radiotherapy Interactions: Numerous studies have shown that radiomimetic drugs such as actinomycin D,[104-107] bleomycin,[107,108] cyclophosphamide,[106,107] and doxorubicin,[107,109] and multiple radiomimetic drug regimens[110] magnify the damaging effects of radiation on the lung. Although doxorubicin is not considered a direct pulmonary toxin, it adds to the toxic effects of radiation.[9] In a study by Verschoore et al,[111] 13 of 24 patients treated with low-dose doxorubicin and chest radiation (40 Gy in 10 fractions) developed pneumonitis.

Chemotherapy-Chemotherapy Interactions: Toxicity is seen at much lower doses than expected when certain drugs are used in combination. Synergism is particularly problematic when nitrosoureas and cyclophosphamide are used together.[9] As described above, concomitant use of bleomycin and other chemotherapeutic agents, such as cyclophosphamide, vincristine, doxorubicin, or methotrexate magnifies the risk of bleomycin-induced fibrosis.[7]

Other Risk-Based Factors for Lung Damage

Skeletal growth defects, such as thoracic hypoplasia, scoliosis, and/or kyphosis, are common late effects among children receiving radiotherapy and could reduce lung volumes, resulting in restrictive lung disease. Among 787 children from the National Wilms' Tumor Study 1 and 2 (1969 to 1979), Evans et al[112] reported that the prevalence of scoliosis was nearly seven times higher in those children receiving radiotherapy (61.4%) than in those who did not (9.4%). Paulino et al[113] reported that the actuarial incidence of scoliosis at 5, 10, and 15 years after radiotherapy (10-40 Gy) in 55 children treated for Wilms tumor was 4.8% ± 3.3%, 51.8% ± 9.0%, and 56.7% ± 9.3%%, respectively.

Table 5—*Studies of Pulmonary Sequelae After HSCT Among Surviving Children*

Study	Patient Population	HSCT Types	Patient Age	Pretransplant Condition	Follow-up	PFT Abnormalities
Serota et al[40]	Acute leukemia (n = 17) and AA (n = 8)	Allogeneic	Median age for ALL:11 y (4-24 y); median age for AA: 14.5 y (2.5-21 y)	CY, TBI, Ara-C	36 mo (27-63 mo)	9/17 had reduced lung volume (< 80% predicted) after 3 mo HSCT
Stokes et al[41]	11 childhood cancer survivors who had severe pneumonia	No reports	11.8 ± 6.2 y	Varied	11 y	3 pts (27%) had significant RLD, with TLC 62%-69% predicted. No OLD was noted. DLCO was reduced in 2 pts on follow-up
Uderzo et al[42]	44 children with various Dx	Allogeneic (n = 34); 9 autologous; 1 unrelated	Median: 9 y 2 mo (1 y 8 mo-18 y)	CY, TBI, busulfan	33 mo (12-114 mo)	PFT abnormality (8: restrictive; 4: obstructive; 2 mixed)
Arvidson et al[43]	29 children with hematologic malignancies	Autologous	Median: 9.8 y (1.9-17.8 y)	TBI ± CY	4.1 y (1.1-7.6 y)	TLC, VC, and FEV_1 were 11%, 13%, and 15% lower than prior to HSCT, but there was an improvement after 6 mo follow-up. But the mean values were 5%-10% lower than baseline in the TBI + group and remained throughout the follow-up period.
Schultz et al[44]	Subset of 67 children survivors (ALL, AML, AA/FA, others)	Allogeneic	Mean: 7.4 ± 4.7	TBI, CY/busulphan/ vincristine/VP-16/ cisplatin/melphalan	7.5 mo (3-55 mo)	FEV_1, $FEF_{25\%-75\%}$, DLCO lower; 29% (10/35) pts with chronic GVHD developed obstructive lung disease compared with none of 32 pts without chronic GVHD
Kaplan et al[45]	AA (n = 14); ALL (n = 29); acute lymphoma (n = 3)	Allogeneic (n = 45)	Mean: 11.7 y (2.7-24.4 y)	TBI, CY, Ara-C, melphalan	2.2 y (0.4-7 y)	FVC, FEV_1, $FEF_{25\%-75\%}$ reduced from pre-HSCT to 9-12 mo and in FVC and FEV_1 reduced from pre-HSCT to 18-24 mo after HSCT in pts with acute leukemia or lymphoma
Rovelli et al[46]	28/51 long-term surviving children (ALL, ANLL, CML,RAEB)	Allogeneic (n = 25) autologous (n = 3)	Median age at HSCT: 9.5 y (6-18 y)	TBI, CY, vincristine/ busulfan/Ara-C	4 y	All variables of PFTs remained within normal limits (80% predicted)
Nenadov Beck et al[47]	38 surviving children primarily for neuroblastoma, NHL, and Ewings sarcoma	Autologous	6.9 y (9 mo-17 y)	BCNU/busulfan/CY	6.9 y (3-11.5 y)	47% were abnormal with restrictive pattern; no obstructive disease was found
Nysom et al[48]	25/29 surviving children with leukemia or lymphoma	Allogeneic	Median age at HSCT: 11.3 y (5.7-17.6 y)	TBI + CY	7.5 y (4-12.6 y)	Pts had significantly reduced transfer factor, TLC, and FVC (−1.0, −1.2, and −0.8 SD score) at median of 7.5 y of follow-up; the restrictive pattern changes persisted for a median of 7.5 y after HSCT

(Continued)

Table 5—*Continued*

Study	Patient Population	HSCT Types	Patient Age	Pretransplant Condition	Follow-up	PFT Abnormalities
Fanfulla et al[49]	39/47 surviving children with ALL, AML, CML, NHL	Allogeneic (n = 29); autologous (n = 10)	Age at HSCT: 12 y	TBI + CY/melphalan/ busulfan/BCNU/ vincristine	3-18 mo	At 18 mo, progressive recovery of lung function was observed, although > 50% of pts developed restrictive pattern with impairment of diffusion capacity
Nève et al[50]	18/41 surviving children with stage IV neuroblastoma	Autologous	Age at TBI: 1.5-6.9 y	TBI + CY/melphalan/ busulfan/BCNU/ vincristine	4 y (1.25-7.6 y)	2/18 had Dlco < 65% predicted; 3/18 had FRC < 65% predicted (restrictive pattern defect)
Cerveri et al[51]	52 children with ALL (n = 25), AML (n = 22), CML (n = 5)	Autologous (n = 19) allogeneic (n = 33)	Mean age at HSCT: 9 y (2-17 y)	TBI ± busulfan, BCNU, amsacrine, Ara-C, VP-16	5 y (3-11 y)	23% had restrictive pattern; 0% obstructive; 15% transfer factor impairment
Leneveu et al[52]	39 children with ALL (n = 16), others (n = 23)	Autologous (n = 16) allogeneic (n = 23)	Mean age: 9.4 y (3.5-17.4 y)	Varied	2.3 y (0.3-8.5 y)	Some of the observed abnormalities were present before HSCT; after HSCT, VC, TLC, and FEV_1 were lower compared with pre-HSCT, but not clinically relevant
Griese et al[53]	138 children with various Dx	Autologous (n = 30)	Median age: 8.6 y (1.1-22.4 y)	Radiation combined with chemotherapy (n = 82); chemotherapy alone (n = 56)	…	85/138 showed a mild restrictive pattern
Cerveri et al[54]	75 children with ALL (n = 37), AML (n = 33), CML (n = 5)	Autologous (n = 23) allogeneic (n = 52)	Median age at HSCT: 11 y (6-19 y)	TBI ± melphalan, thiotepa, CY	3-24 mo	Before HSCT, at 3-6 mo after HSCT, and at 24 mo after BMT, 44%, 85%, and 62% of children, respectively, had altered lung function in the absence of persistent respiratory symptoms; between 3 mo and 6 mo after HSCT, a restrictive pattern was the most frequent abnormality
Bruno et al[55]	80 surviving children with various Dx	Allogeneic	Median age at HSCT: 9 y (3-18 y)	Varied	4 y (1-10 y)	FEV_1 and FVC were lower (−8% and −7%) at 2 y after HSCT; FEV_1/FVC ratio decreased in pts with chronic GVHD from 4 to 10 y after HSCT
Frisk et al[56]	26 children with acute leukemia or lymphoma	Autologous	TBI group median 8.6 (3.6-17.7); -TBI group (n = 6) 9.6 (1.9-15.2)[a]	Varied	10 y (5-10 y)	Lung volumes and Dlco reduced immediately after HSCT, but recovered partially and stabilized over subsequent y, so little changes in PFT values 1-10 y post HSCT.
Faraci et al[57]	42/134 children receiving TBI, neuroblastoma (n = 14), ALL (n = 14), AML (n = 11), NHL (n = 3)	Autologous (n = 26) allogeneic (n = 16)	Median age at TBI: 6.3 y (1.1-16.2 y)	Varied	18.4 y (13.2-28.1 y)	PFT abnormalities (n = 30) (74%) at median 3.1 y follow-up. (restrictive pattern) (0 obstructive); 45% (n = 19) showed permanent mild restrictive insufficiencies

(Continued)

Table 5—*Continued*

Study	Patient Population	HSCT Types	Patient Age	Pretransplant Condition	Follow-up	PFT Abnormalities
Hoffmeister et al[58]	215/472 patients with hematologic malignancy (n = 175) and nonhematologic malignancy (n = 40)	Autologous (n = 13) allogeneic (n = 202)	Age at HSCT: 8.3 y (0.3-18.0 y)	Varied	10 y	60 (28%) of pts had RLD, 19 (9%) OLD, and 7 (3%) mixed RLD/OLD; a low- DLCO was observed in 77 (43%) of 162 pts who performed diffusing capacity studies
Leung et al[59]	155 patients after receiving HSCT: myeloid malignancy (n = 84), lymphoid malignancy (n = 40), nonmalignancy (n = 31)	Allogeneic	Age at HSCT: 9.7 y (0.5-21.4 y)	TBI-based (n = 123); Alkylator-based (n = 32)	9 y	Cumulative incidence of PFT abnormalities at 10 y post-HSCT was 63%; TBI, female sex, and thiotepa exposure were communal risk factors for RLD, OLD, and abnormal DLCO.
Efrati et al[60]	90 children with nonmalignant (n = 16), solid (n = 10), HD (n = 47), AML (n = 3), ALL (n = 14)	Allogeneic	Age at Dx: 12.6 ± 6 y	Varied	≤ 5 y	30 pts presented mildly reduced flows and lung volumes; n = 7 presented severely reduced flow; 7/53 presented pulmonary symptoms; n = 12 presented lower DLCO
Ricardi et al[61]	51 surviving children with hematologic malignancies	Allogeneic (n = 32); autologous (n = 19)	Median age at HSCT: 8.5 y (2-16.4 y)	TBI + chemotherapy	8.6 y (5.1-17.9 y)	14/32 allogeneic HSCT pts developed chronic GVHD; 6 pts showed restrictive (4 mild, 2 severe), one obstructive
Inaba et al[62]	89 surviving children with hematologic malignancies	Allogeneic	Mean age at HSCT: 12.7 y (6.6-21.3 y)	Varied	8.9 y	Progressive worsening of PFTs measured $FEF_{25\%-75\%}$, RV, TLC, and DLCO during a median follow-up of 8.9 y

AA = aplastic anemia; AML = acute myeloid leukemia; ANLL = acute nonlymphocytic leukemia; Ara-C = cytosine arabinoside; CML = chronic myeloid leukemia; CY = cyclophosphamide; Dx = diagnosis; FA = Fanconi anemia; $FEF_{25\%-75\%}$ = forced midexpiratory flow; OLD = obstructive lung disease; RAEB = refractory anemia with excess of blasts; RLD = restrictive lung disease; VC = vital capacity; VP-16 = etoposide. See Table 1 to 3 legends for expansion of other abbreviations.

[a]+TBI group includes the children who received fractonated TBI (12 Gy). –TBI group includes the children who received BCNU, etoposide, cytarabine, and cyclophosphamide.

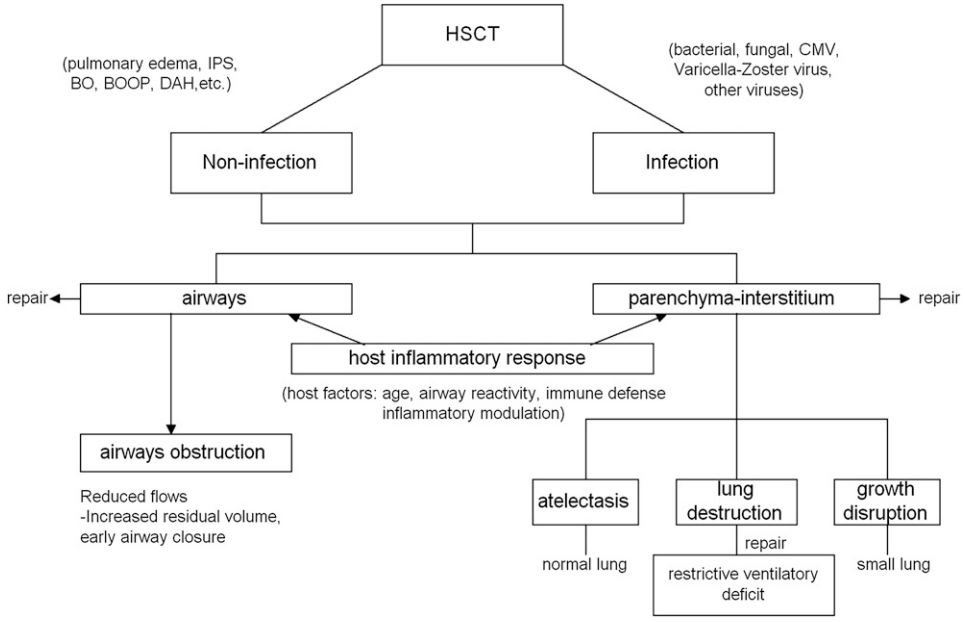

FIGURE 1. Mechanisms for altered pulmonary function and/or growth by HSCT. BO = bronchiolitis obliterans; BOOP = bronchiolitis obliterans organizing pneumonia; CMV = cytomegalovirus; DAH = diffuse alveolar hemorrhage; HSCT = hematopoietic stem cell transplant; IPS = idiopathic pneumonia syndrome.

In addition to their therapeutic exposure to agents designed to treat their disease, children with cancer may have other risk factors that predispose them to long-term pulmonary problems. These include genetic susceptibility to chemotherapy or radiation, underlying asthma or chronic obstructive lung disease, infection, cigarette use, and exposure to environmental respiratory toxins. The effect of early childhood injury during cancer therapy in accelerating the normal decline in lung function that occurs with aging is an important area for future research.

Limitations

Our review was limited to studies requiring a minimum of 2 years follow-up after completion of cancer-related treatment, and early-onset pulmonary complications related to anticancer modalities were not discussed. Another limitation was that most conclusions in this review were based on prospective serial evaluations, retrospective chart reviews, and cross-sectional investigations in a small cohort in one or multiple institutions. The data from the included studies were limited to published studies. Additionally, it is likely that selection bias is possible because we excluded two articles because their full texts were not available.

CONCLUSIONS

In this systematic review of literature from 1970 to 2010 focused on the known and potential pulmonary late effects among survivors of childhood cancer, the evidence indicates that some treatments necessary to cure malignancy contribute to long-term pulmonary dysfunction. Individual and combined treatment exposures to radiotherapy, bleomycin, alkylating agents, HSCT, and thoracic surgery increase the risk of later lung diseases. Understanding the late effects that result from specific treatment exposures, the contributions of the interactions among therapeutic modalities, and the natural history of evolving pulmonary morbidity over time provides information about host and therapy-related factors that adversely affect outcome.

Although current knowledge facilitates awareness of adverse pulmonary outcomes and identification of high-risk groups, additional investigation is required on many fronts. First, exploring the genetic susceptibility to adverse pulmonary outcomes may provide more information about populations whose risk of a poor outcome precludes use of a particular agent during treatment.[114,115] Genetic factors may also influence the interaction of therapeutic exposures with lifestyle exposures such as tobacco. Second, progress in understanding the underlying molecular mechanisms that predict pulmonary toxicity post therapy may foster the development of early detection methods and allow early treatment among specific groups of survivors of childhood cancer. For example, several predictive markers of radiation pneumonitis, such as transforming growth factor-β1, interleukins, and implicated adhesion molecules have been identified as potentially useful.[116,117] Third, cancer

survivorship research is a field that is evolving as new agents, different drug combinations, and altered chemotherapy-radiotherapy sequencing are being tested. Evaluation of the late effects of these exposures will need to be conducted to determine outcomes with more contemporary therapies. Fourth, advances in supportive care, including transfusions and hematopoietic growth factors, also require ongoing surveillance to identify pulmonary late effects. By outlining our current understanding of pulmonary toxicity in childhood cancer survivors and suggesting topics for future research, we hope that this review will serve as a stimulus for the expansion of knowledge about this important aspect of cancer survivorship.

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