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PENTEC ORGAN SYSTEM REVIEW

Idiopathic Pneumonitis Syndrome After Total Body Irradiation in Pediatric Patients Undergoing Myeloablative Hematopoietic Stem Cell Transplantation: A PENTEC Comprehensive Review

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Purpose: Pulmonary complications, especially idiopathic pneumonitis syndrome (IPS), are potentially life altering or fatal sequelae of hematopoietic cell transplantation (HCT). Total body irradiation (TBI) as part of the conditioning regimen has been implicated in IPS. A comprehensive PENTEC (Pediatric Normal Tissues in the Clinic) review was performed to increase our understanding of the role of TBI in the development of acute, noninfectious IPS.

Methods and Materials: A systematic literature search was conducted using the MEDLINE, PubMed, and Cochrane library databases for articles describing pulmonary toxicity in children treated with HCT. Data pertaining to TBI and pulmonary endpoints were extracted. Risk of IPS was analyzed in relation to patient age, TBI dose, fractionation, dose rate, lung shielding, timing, and type of transplant, with the goal to better understand factors associated with this complication in children undergoing HCT. A logistic regression model was developed using a subset of studies with comparable transplant regimens and sufficient TBI data.

Results: Six studies met criteria for modeling of the correlation of TBI parameters with IPS; all consisted of pediatric patients undergoing allogeneic HCT with a cyclophosphamide-based chemotherapy regimen. IPS was variably defined, but all studies that reported IPS were included in this analysis. The mean incidence of post-HCT IPS was 16% (range, 4%-41%). Mortality from IPS, when it occurred, was high (median, 50%; range, 45%-100%). Fractionated TBI prescription doses encompassed a narrow range of 9 to 14 Gy. Many differing TBI methods were reported, and there was an absence of 3-dimensional dose analysis of lung blocking techniques. Thus, a univariate correlation between IPS and total TBI dose, dose fractionation, dose rate, or TBI technique could not be made. However, a model, built from these studies based on prescribed dose using a normalized dose parameter of equivalent dose in 2-Gy fractions (EQD2), adjusted for dose rate, suggested correlation with the development of IPS ($P = .0004$). The model-predicted odds ratio for IPS was 24.3 Gy^{-1} (95% confidence interval, 7.0-84.3). Use of TBI lung dose metrics (eg, midlung point dose) could not be successfully modeled, potentially because of dosimetric uncertainties in the actual delivered volumetric lung dose and imperfections in our modeling process.

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Conclusions: This PENTEC report is a comprehensive review of IPS in pediatric patients receiving fractionated TBI regimens for allogenic HCT. IPS was not clearly associated with 1 single TBI factor. Modeling using dose-rate adjusted EQD2 showed a response with IPS for allogeneic HCT using a cyclophosphamide-based chemotherapy regimen. Therefore, this model suggests IPS mitigation strategies can focus on not just the dose and dose per fraction but also the dose rate used in TBI. More data are needed to confirm this model and to determine the influence of chemotherapy regimens and contribution from graft-versus-host disease. The presence of confounding variables (eg, systemic chemotherapies) that affect risk, the narrow range of fractionated TBI doses found in the literature, and limitations of other reported data (eg, lung point dose) may have prevented a more straightforward link between IPS and total dose from being observed.

Introduction

Total body irradiation (TBI) is often part of the preparative regimen in hematopoietic cell transplantation (HCT) because of its myeloablative, tumoricidal, and immunosuppressive effects.

This review is focused on the pulmonary toxicity associated with TBI in the context of HCT. This is distinct from other settings in which partial lung or whole lung are irradiated (eg, metastatic Wilms sarcomas), because lung injury in the context of HCT can also be influenced by the chemotherapy conditioning regimen and the development of graft-versus-host disease (GVHD).

Clinical Significance

One of the most life-threatening early toxicities after TBI-based HCT is noninfectious idiopathic pneumonitis syndrome (IPS). IPS can be attributed to TBI, HCT conditioning chemotherapy, GVHD,[1-3] and/or occult pulmonary infections.[4] The underlying mechanisms may involve a cytokine-mediated inflammatory immune response that leads to injury of the pulmonary parenchyma, vascular endothelium, and/or airway epithelium.[5] Clinical features of IPS may mimic those of pneumonia, presenting as dyspnea, hypoxemia, fever, but without identifiable infectious etiologies. Table 1 lists the terminologies and definitions of noninfectious acute pulmonary toxicities of the included studies. For the purpose of the current review, interstitial pneumonitis and IPS are considered synonymous.

IPS is generally considered to occur within the first 120 days after allogeneic HCT. In a study of 251 pediatric HCT patients in which 8% developed IPS, the median time to pneumonitis was 67 days, and the patients who developed IPS had higher 5-year transplant-related mortality (52% vs 13%) and lower overall survival (42% vs 68%) than those for whom it did not occur.[1]

Data are limited for effective management of IPS in pediatric patients in the post-HCT setting. A joint study from

Table 1 Definition of noninfectious acute pulmonary toxicities among the included studies

Study first author	Toxicity terminology	Definition
1. Abugdideiri[24,*]	PT, IPS	Same criteria as ATS definition
2. Abdeljelil[19]	IP	Not given (infectious sources classified separately)
3. Bradley[52,*]	IP, idiopathic IP	Either clinical signs or radiographic interstitial infiltrates
4. Coccia[42]	Idiopathic diffuse IP	Not given
5. Dusenbery[45]	IP	Not given
6. Gao[20,*]	IPS	Cited ATS definition[5]
7. Kim[21,*]	PT	Cited Abugideiri et al[24]
8. Kurisu[53]	IP	Hypoxemia and nonlobar infiltrate on imaging in the absence of congestive heart failure or infection
9. Petersen[22]	Radiation-induced IP	Not given; some infectious sources excluded
10. Spitzer[54,*]	Idiopathic IP	Not given
11. Weshler[23,*]	IP, idiopathic IP	Dyspnea or cough >30 d after HCT; infiltrates on x-ray without evidence of infection Idiopathic IP = absence of infection and no response to antibiotics
12. Wingard[46]	IP	Hypoxemia and nonlobar infiltrate on imaging in the absence of congestive heart failure or infection

Abbreviations: ATS = American Thoracic Society; EQD2 = equivalent dose given in 2-Gy fractions; HCT = hematopoietic cell transplantation; IP = interstitial pneumonitis; IPS = idiopathic pneumonia syndrome; PT = pulmonary toxicity.
* Studies included in dose-rate corrected EQD2 model.

the Pediatric Blood and Marrow Transplant Consortium and Children's Oncology Group (COG) demonstrated that pediatric patients (<18 years of age) meeting criteria for IPS within 120 days after HCT derived clinical benefit when treated with systemic corticosteroids (2 mg/kg/d) in combination with the tumor necrosis factor receptor inhibitor etanercept (0.4 mg/kg twice weekly for 8 doses).[6] Among evaluable patients, 71% achieved a complete response, and the median time to complete response was 10 days (range, 1-24 days).

Survivors of HCT can have a variety of lung conditions, such as restrictive lung disease, impaired gas exchange, and obstructive lung disease (OLD). OLD is more commonly caused by chronic GVHD and less likely from IPS and results in a high mortality. Lung volumes have been documented to decline from baseline during the 6 months that follow HCT.[7,8] Partial recovery may occur over 1 to 2 years.[9-11] In a study of allogeneic pediatric HCT (N = 228), the majority of the late lethal pulmonary complications were due to infectious etiologies.[12]

HCT conditioning regimens can be classified as myeloablative, reduced intensity, or nonmyeloablative.[13] Myeloablative conditioning regimens containing TBI generally use ≥5 Gy in a single fraction or ≥8 Gy fractionated over 3 or 4 days, while nonmyeloablative regimens typically use 2 to 4 Gy given in 1 or 2 fractions.[13,14]

Methods of delivering TBI have historically been institution-driven[15,16] and administered with either cobalt units or linear accelerators. Anterior-posterior (AP/PA) fields and right-left lateral fields are examples. AP/PA treatments can be delivered with patients either standing or reclined in a decubitus position with variable applications of lung compensation/shielding techniques. Before the 1990s, myeloablative TBI was typically delivered in a single fraction, but this has now been largely abandoned and replaced with fractionated regimens that are associated with fewer short- and long-term side effects. We did not include studies using single fraction TBI regimens in this review as these older trials predate the vast improvements in donor selection, GVHD prevention, and identification of infectious agents, that is, factors that can confound the role of TBI in IPS. Fractionated myeloablative TBI doses generally range from 9 to 14 Gy with dose per fraction of 1.2 to 3.3 Gy, given once, twice, or even 3 times each day. TBI dose rates range from 4 to 50 cGy/min. Recently, there has been an increase in the utilization of rotational intensity modulated radiation therapy (IMRT) techniques for TBI; with these techniques, the instantaneous dose rate for any specific tissue may greatly exceed the dose rates studied in this work.

A detailed understanding of the relationship of TBI dosimetric parameters (eg, dose, fractionation, and dose rate) and other treatment related factors (eg, chemotherapy regimen) on the development of IPS would help to inform TBI-containing regimens for HCT among pediatric patients.

Endpoints and Toxicity Scoring

IPS is the acute clinical endpoint for this review. Criteria for IPS were variable in the reported literature and in some cases not defined. Despite the variability, IPS rates were analyzed as reported because no further discernment of the reported IPS rates was possible. Because IPS is not graded in the reported literature, this report treats IPS as a binary endpoint, either IPS or no IPS, as defined by each study (Table 1).

For survivors of HCT, late pulmonary toxicity has been described in the literature with multiple endpoints, including restrictive lung disease, OLD, and symptomatic breathing impairments such as shortness of breath or requirement of supplemental oxygen. Some reports do not define clinical syndromes but, rather, report pulmonary function test (PFT) results such as forced vital capacity, forced expiratory volume in 1 second, and so forth. Post-HCT PFT results can be affected by many factors unrelated to the preparative regimen, for example, infections, smoking, and GVHD.

IPS toxicity grade has not been frequently reported in the literature; rather it has been defined as IPS or non-IPS. However, the Common Terminology Criteria for Adverse Events (CTCAE), version 5 (https://ctep.cancer.gov), scale should be used to grade pulmonary toxicity.

Anatomy and Developmental Dynamics

Understanding the age-specific development of the lungs might shed light on the potential for increased risk for pulmonary complications in younger children. Formation of the airways starts in the prenatal embryonic phase of fetal development. Bronchial branching is complete by the end of gestational week 16. Alveoli develop and can support air exchange by week 24 but continue to develop until birth and even into the first months of postnatal life. As growth of the thoracic cage continues, the size of the lung tissue expands proportionally.[17] The effect of these developmental changes on the risk for IPS after HCT has not been studied and would be difficult because TBI-based HCT is rarely used in infants. Later on, the greatest rate of growth is observed during puberty. Along with the increase in growth, lung function improves with the increase in elastic recoil of the lungs. Lung function is affected by genetic factors, nutrition, activity, hormones, and environmental factors.[18]

Defining Volumes: Pediatric Imaging Issues

None of the studies included in this analysis used volumetric-based (eg, computed tomography [CT]) treatment planning. Lung dose was estimated based on dose at a point usually midplane in the midlung using AP and lateral chest radiographs and bony anatomy. Radiographs are typically used for designing lung compensators/blocks for AP/PA

treatment techniques. The description of the blocking (if any) and details of tissue compensators (if used) were scant. Further discussion related to the effect of lung blocking techniques is included in Review of Dose: Volume Data.

Review of Dose-Volume Response and Risk Factors

Search methodology

A systematic literature search was conducted using the MEDLINE, PubMed, and Cochrane library databases via search terms related to TBI and HCT. English language reports from 1980 to 2017, either with all patients ≤21 years of age or containing a cohort with a median age ≤21 years, were eligible. A representation of search terms is provided in Appendix E1.

To be considered for modeling of TBI effects on IPS, studies were required to provide sufficient information such that the total dose to the prescription point and a point in the midlung (if lung blocking was used), as well as the associated dose rate, could be determined. Studies reporting nonmyeloablative doses (eg, total dose of 2-4 Gy) were excluded. As current practice frequently uses fractionated regimens with a fraction size of 2 Gy or less, reports that used twice daily fraction with each dose 2 Gy or less or once daily fraction with each dose 3 Gy or less were included, and those using larger fraction doses were omitted. Additional criteria for inclusion in modeling were >50% of all patients with allogeneic stem cell source, >50% of patients received cyclophosphamide-based chemotherapy regimen, and >20 patients in an identified group for which IPS was reported.

In total, 3049 studies were identified in the literature search, of which 3003 were excluded based on title/abstract review. Three additional reports[19-21] were included after the 2017 literature search was conducted, for a total of 49 initially included studies. One study included both adult and pediatric patients; however, the pediatric population was able to be separately analyzed (by the authors), allowing the data to meet age criteria for inclusion.[20] Of the 49 initially included studies, only 12 had sufficient TBI and IPS data (see Appendix E2 for the excluded studies). Six of the 12 studies were excluded from modeling because of stem cell source, chemotherapy regimen, or sample size not meeting eligibility criteria for modeling (listed in Table 2 for completeness). The remaining 6 studies were used in modeling and met the criteria of sufficient patient numbers (>20), allogeneic stem cell source, conditioning with cyclophosphamide-based therapy, and sufficient TBI and IPS data (Table 3).

Among the 49 initially included studies, 8 reports contained information relevant to lung function in posttransplant survivors. PFT, as a measure for lung injury, was generally performed at baseline and then at various intervals after HCT. However, none of these 8 late toxicity studies described the TBI methods to a degree that would allow analysis of the effect of TBI on PFT, so for this review, a summarization of the available PFT data are provided (Table 4).

TBI-specific parameters were extracted, including total prescribed dose, total lung dose, fractionation schedule, beam energy, dose rate at the prescription point, midlung dose rate, and patient positioning. Additional patient and treatment-related factors such as age, chemotherapy regimen, and donor source were also recorded (Tables 2-4).

Modeling

A population of 457 patients, across 6 studies, were pooled for analyses of the effect of TBI factors on the incidence of IPS (Table 3). For studies that included multiple TBI regimens (ie, multiple total doses and/or more than 1 dose rate) with separately reported IPS, each patient group was treated as a separate cohort, resulting in 10 total cohorts. Dosimetric data were collected for the prescription point and for a midlung dose calculation point. Dose rates were typically reported as the instantaneous dose rates at the prescription point. Midlung dose rates were determined by multiplying the prescription dose rate by the ratio of the midlung total dose to the prescription point total dose.

Review of Dose: Volume Data

Within the 6 studies (providing a total of 10 patient cohorts) included in the statistical modeling, the reported incidence of IPS ranged from 4% to 41% with a mean of 16%, and among those with IPS the mortality rate ranged between 45% and 100% (median, 50%).

Incidence of IPS and total TBI dose and dose rate

Dose

The mean prescribed TBI dose was limited to a relatively narrow range (10.9-13.2 Gy). From the evaluated studies, an IPS-dose response relationship was not found for either the total prescribed dose (Fig. 1a) or the total midlung dose (Fig. 1b) on a purely physical total dose basis. However, we cannot conclude that total dose is inconsequential because the range of doses assessed was narrow, the data are limited, and there are other factors that affect the risk of IPS that confound the analysis.

Indeed, within individual studies, there is evidence of a dose response for IPS. One study (not included in the model; Table 2) attempted to establish the maximum tolerated TBI dose (given in 2-Gy fractions twice per day) in a dose escalation fashion without lung blocking.[22] This study suggested a steep dose response relationship for TBI-associated grade 3 to 4 toxicity, which occurred in 1 of 8, 0 of 4, 3 of 20, and 2 of 4 patients receiving a total of 12, 14, 16, and

Table 2 Details of TBI dosimetry and estimated physical dose for studies excluded for modeling

Study first author (accrual years)	N	IPS rate (%)	Total prescription dose (Gy)	Dose fraction (Gy)	Dose rate (cGy/min)	Delivery technique	Lung blocking method and estimated midlung dose	Transplant source and chemotherapy	Model exclusion reason
Abdeljelil[19] (2003-2013)	87	2	9.9	3.3 QD	4.5	Custom cerrobend protection of lungs on second fraction	Partial transmission to keep lung dose ≤9.0 Gy	Allogeneic with Etop (90%) or CY (10%)	CY <50% cases
Coccia[42] (1981-1986)	20	10	12.0	2.0 bid	15-20	6 or 15 MV lateral, midline umbilicus "limit off axis dose to 12 Gy"	None 12.0 Gy estimated	Allogeneic with ARA-C	CY <50% cases
Dusenbery[45] (1987-1993)	18	6	13.2	1.65 bid	10	6, 10, 24 MV semirecumbent laterals, prescribed to midplane at umbilicus	Compensators 13.2 Gy estimated	Autologous with CY	Autologous
Kurisu[53] (1984-1989)	13	31	12.0	2.5 QD	10	10 MV lateral supine: treated 1 side with 180° rotation every other day	Compensators 12.0 Gy	Allogeneic with CY	Population <20
Petersen[22] (not defined)	36	Variable	12.0-17.0	2.0 bid	8	Dual opposing ^{60}Co sources; 17 Gy treated in 2-Gy fractions to 16 Gy, then additional 1-Gy fraction	None 12.0-17.0 Gy	Allogeneic with CY	Population <20
Wingard[46] (1976-1985)	91	8	8.0, 12.0, 14.4	8.0, 3.0, 1.8	5.0-7.5	^{60}Co AP/PA: blocking only during part of treatment 3 Gy QD × 4 most common	Partial blocking 8.0, 9.0, 10.8 Gy	Autologous with CY	Autologous

Abbreviations: AP/PA = anterior-posterior; ARA-C = cytosine arabinoside; bid = twice per day; CY = cyclophosphamide; Etop = etoposide; IPS = idiopathic pneumonia syndrome; QD = once per day; TBI = total body irradiation.

Table 3 Details of TBI dosimetry and estimated physical dose for studies included in modeling

Study first author (accrual years)	N	IPS rate (%)	Dose rate (cGy/min)	Total prescription dose (Gy)	Dose fraction (Gy)	Delivery technique	Lung blocking method and estimated midlung dose	Transplant source and chemotherapy
Abugdideiri[24] (2003-2014)	124			10.5-14	1.5-2.0	6 MV lateral decubitus and AP/PA Prescription at umbilicus	Partial transmission blocks to keep lung dose to 8-10 Gy	Allogeneic with CY or CY+
Cohort 1	57	12	7.5					
Cohort 2	23	13	12.5					
Cohort 3	44	41	17.5					
Bradley[52] (1985-1994)	77	4	12	12.0-13.5	1.2 tid 2.0 bid	24 MV supine on modified table with 2 lateral fields	88% transmission blocks to keep lung dose ≤12 Gy	Allogeneic with CY+
Gao[20] (2006-2016)	91			13.2	1.65 bid	6, 18 MV semirecumbent laterals, prescribed to midplane at umbilicus	Compensators 13.2 Gy	Allogeneic with CY
Cohort 1	45	7	11					
Cohort 2	46	35	17					
Kim[21] (2000-2016)	77				3.0 QD	6, 15 MV lateral decubitus and AP/PA 5%-10% compensator on AP and arms used to compensate on PA	Compensators 9.0-12.0 Gy	Allogeneic with CY+
Cohort 1	23	9	4.8	11.7				
Cohort 2	54	22	8.6	10.9				
Spitzer[54] (1987-1990)	44	5	26	12.0-13.2	1.2-2.0 bid	6, 10, 25 MV AP/PA techniques at 3 centers	Lung block after 10 Gy at 2 centers, no lung block for 13.2 Gy at third center	Allogeneic CY + Etop (66%) or autologous CY + Etop (34%)
Weshler[23] (1983-1987)	44	14	18	9.0-12.0	2.0 bid	6 MV fetal position laterals or AP/PA with 50% transmission block after 6 Gy	Lateral 12.0 Gy, AP/PA 9.0 Gy	Allogeneic with CY (86%) or autologous with CY (14%)

Abbreviations: AP/PA = anterior-posterior; bid = twice per day; CY = cyclophosphamide; CY+ = cyclophosphamide plus other agent(s); Etop = etoposide; IPS = idiopathic pneumonia syndrome; QD = once per day; TBI = total body irradiation; tid = 3 times per day.

Table 4 PFTs after HCT

Study first author	Median time post-HCT in years (range)	N	TBI details	Findings	Risks associated with PFT decline
Hoffmeister[8]	10 (5-27)	215	Various	RLD, OLD, or low DLCO 55% of cases; moderate to severe RLD and OLD 45%; SOB 15%	Single-fraction TBI (RLD and OLD), diagnosis, scleroderma/contracture, donor source (RLD), GVHD, posttransplant time (OLD)
Frisk[7]	18 (10-22)	18	sfTBI 7.5 Gy or fTBI 12.6 Gy in 6 fx	Increase in RLD from control group and from individual pre-HCT; 5 y post-HCT moderate to severe RLD 20%; at 18 y 55% with DLCO impairment of 61%	
Uhlving[55]	5 (1.5-16.8)	28 10 TBI	No details	LCI few months post-HCT is predictive of respiratory complications at 1 y; LCI and FEV_1 were predictive for chronic GVHD	Abnormal baseline PFT
Nysom[11]	7.5 (4-12.6)	25	sfTBI (8.5 or 10 Gy) or fTBI 11.3 Gy in 3 fx	FVC and TLC decreased in first year, improvement possible later	
Arvidson[9]	Multiple	42	sfTBI 7.5 Gy	Decrease in TLC, FVC, FEV_1 from baseline at 6 mo post-HCT for sfTBI group; some recovery after 6 mo	sfTBI regimen (vs non-TBI regimen) significant for TLC, FVC, and FEV_1 decline
Madanat-Harjuoja[34]	4	51	fTBI 10-14 Gy	59% RLD and OLD; decline in FEV_1 and FVC <1 y, then stable	GVHD and abnormal baseline PFTs
Fanfulla[10]	1.5	39	fTBI 12 Gy in 6 fx	RLD and DLCO 50%; abnormal PFT in 44% of cases at 3 mo, 38% at 18 mo	GVHD, cytomegalovirus seropositivity
Inaba[33]	8.9 (7.7-16.4)	89	fTBI 12-14 Gy in 96%	Abnormal PFT pre-HCT 40%; post-HCT 61%; DLCO, FEV_1/FVC, FEV25-75, and TLC declined over time	Respiratory complication 1 y post-HCT, sex, age, source, and disease risk
Bruno[56]	4 (3-18)	80	fTBI 12 Gy in 6 fx, lung blocking 9 Gy	FVC and FEV_1 decreased 2 y post-HCT	Busulfan-based conditioning regimen (vs TBI); chronic GVHD

Abbreviations: DLCO = diffusion capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; fTBI = fractionated total body irradiation; FVC = forced vital capacity; fx = fractions; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; LCI = lung clearance index; OLD = obstructive lung disease; PFT = pulmonary function testing; RLD = restrictive lung disease; sfTBI = single fraction total body irradiation; SOB = shortness of breath; TBI = total body irradiation; TLC = total lung capacity.

17 Gy, respectively. Unfortunately, the study was of a mixed adult and pediatric population and did not have sufficient pediatric population to include in the modeling.

Similarly, Weshler et al[23] (included in modeling) used 50% transmission lung blocking for the final half of the TBI regimen for a subset of patients (n = 21) and compared them to another subset without transmission lung blocking (n = 23; Table 3), resulting in midlung doses of 9 and 12 Gy, respectively. Although a lower IPS rate was observed for the 9 Gy midlung dose group (0 out of 21 vs 6 out of 23 in the 12 Gy group, as shown in Fig. 1b), this difference did not reach statistical significance, perhaps because of the limited patient numbers. Because the prescribed dose to the rest of the body was 12 Gy in both patient groups, these patients were pooled to a single data point for the prescription dose analysis in Fig. 1a.

Dose rate

Three of the studies[20,21,24] in Fig. 1 have multiple data points, reflecting multiple dose rates with the same total

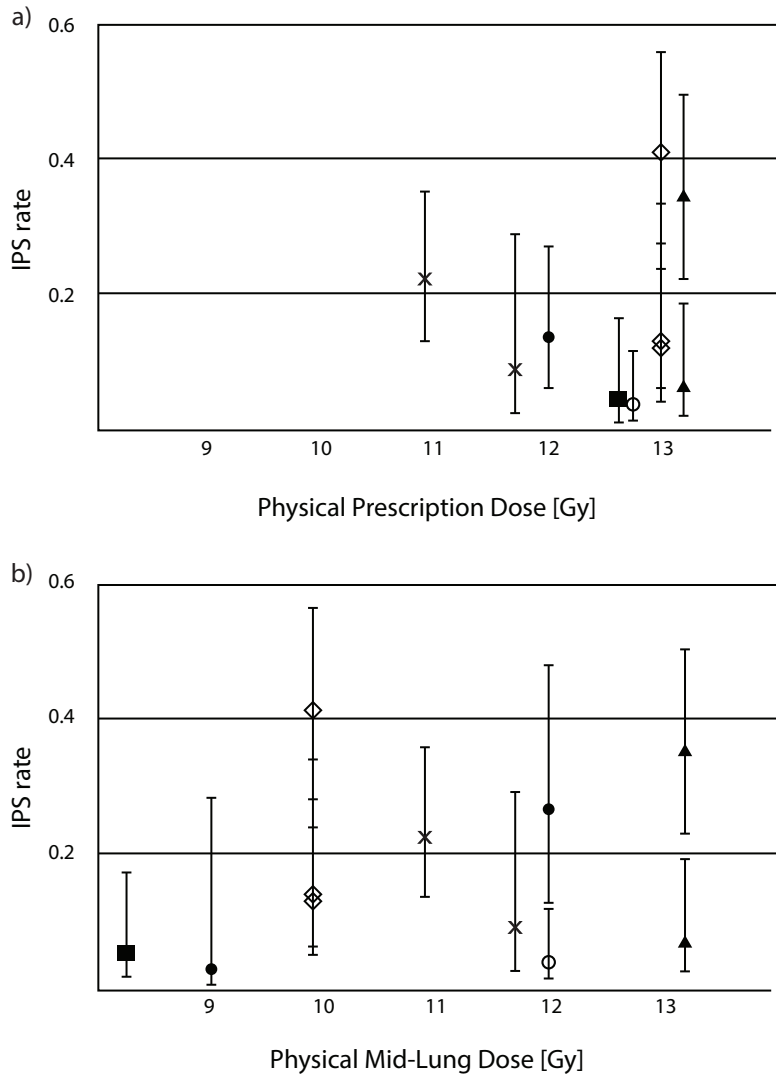

Fig. 1. Idiopathic pneumonitis syndrome versus (a) prescription dose and (b) midlung dose. Individual studies are identified by the following marker types: ◇, Abugdideiri et al[24]; ▲, Gao et al[20]; ×, Kim et al[21]; •, Weshler et al[23]; ■, Spitzer et al[54]; ○, Bradley et al.[52] Studies with more than 1 data point reported multiple dose rate and/or dose cohorts. Error bars show the 95% confidence interval of the cohort.

dose[20,24] or both different multiple dose rates and total doses.[21] All 3 studies observed an increased rate of IPS in the highest dose rate group (Fig. 2) even when the total doses and fraction size remained constant.[20,24] In light of these observations, our IPS response model predictor variable was chosen such that it included total dose, dose per fraction, and dose rate.

Incidence of IPS and dose-rate corrected equivalent dose given in 2-Gy fractions

The 6 studies that met model inclusion criteria summarized in Table 3 were used to create an IPS response model to a normalized biological equivalent dose. To condense several dosimetric factors into a single parameter, a normalized biologically equivalent dose given in 2-Gy fractions (EQD2) was used. The EQD2 parameter was a function of the following: total dose, dose per fraction, and instantaneous dose rate. The EQD2[25] was determined using the following:

$$\mathrm{EQD2} = \mathrm{n}\cdot\mathrm{d}\left(\frac{\mathrm{d}\cdot\mathrm{g}+\alpha/\beta}{2\ \mathrm{Gy}+\alpha/\beta}\right) \quad (1)$$

where n is the number of fractions, d is the dose per fraction in Gy, and α/β (α/β ratio) is a biologic parameter related to the radiation sensitivity of a tissue with units of Gy. The term g accounts for the dose rate[26,27] with the following:

$$\mathrm{g} = \frac{2(\mu\mathrm{t}-1+\mathrm{e}^{-\mu\mathrm{t}})}{(\mu\mathrm{t})^2} \quad (2)$$

where t can be thought of as the "beam-on time" for a single fraction determined by

$$\mathrm{t} = \frac{\text{dose per fraction}}{\text{instantaneous dose rate}} \quad (3)$$

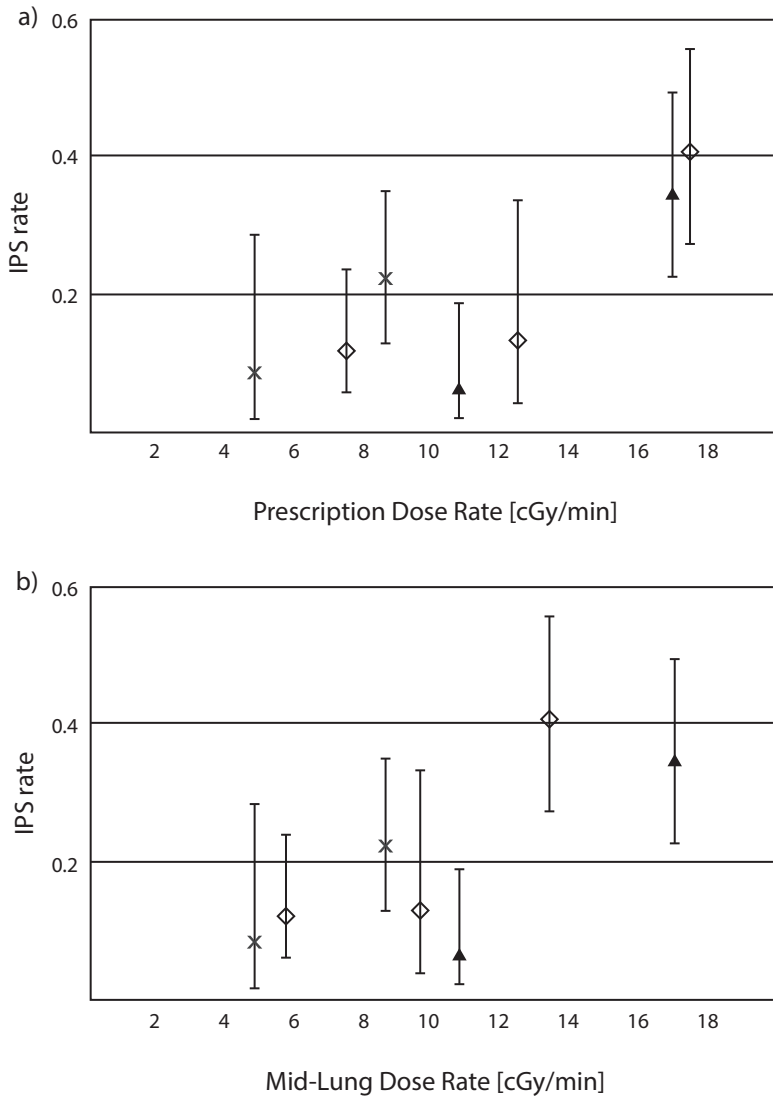

Fig. 2. Idiopathic pneumonitis syndrome versus instantaneous dose rate for the (a) prescription point and (b) midlung. Individual studies are identified by the following marker types: ◇, Abugdideiri et al[24]; ▲, Gao et al[20]; ×, Kim et al.[21] These 3 studies reported idiopathic pneumonitis syndrome for more than 1 dose rate group. Error bars show the 95% confidence interval of the cohort. Abugdideiri et al[24] used lung blocking and thus the data points shift along the x-axis between (a) and (b); the other studies used lung compensation and therefore are the same.

and

$$\mu = \frac{\ln 2}{T_{1/2}} \tag{4}$$

where $T_{1/2}$ is the half-time recovery parameter that describes the rate at which a given tissue can repair radiation damage.[25]

Logistic regression was performed using meta-analysis software (Comprehensive Meta-Analysis V3; Biostat, Englewood, NJ). A random effects model was used, rather than fixed effects, because of the interstudy variability (eg, patient diagnosis, demographics, TBI methods, IPS definitions, chemotherapy regimen, management of GVHD, etc). The Knapp-Hartung method was used, which does not affect the logistic regression coefficients but is considered an accurate estimator of error intervals for heterogeneous data.[28]

The probability, p, of IPS was modeled by logistic regression:

$$p = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x)}} \tag{5}$$

where β_0 is a constant and β_1 is the coefficient of the predictor variable (x), in this case EQD2.

For this work we define lung blocking as a method to reduce the beam intensity to the lungs such that the dose to the midpoint of the lung is less than 90% of the dose prescribed to the rest of the body. Lung compensation is defined as modifying the beam intensity to result in the dose to the midpoint of the lung being within ±10% of the prescription dose. To account for treatments that used lung blocking (and therefore different doses for the lungs than the rest of the body), EQD2 was separately calculated and

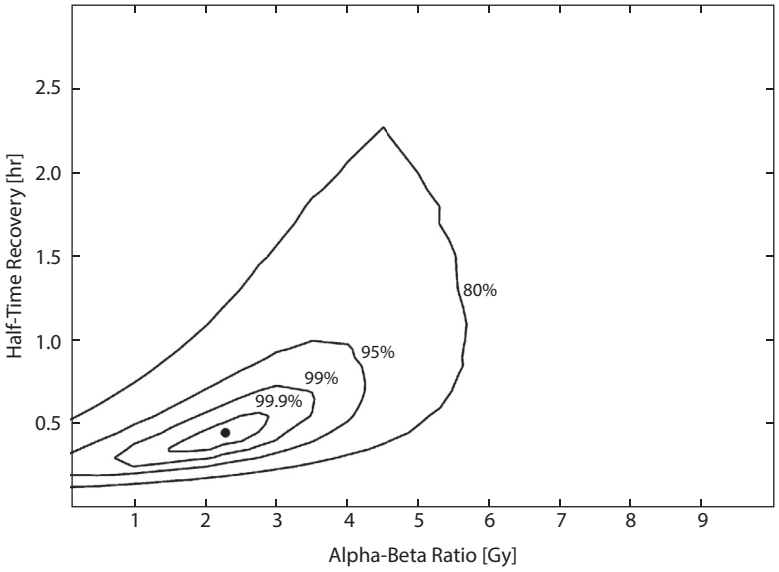

Fig. 3. Likelihood surface plot for the α:β ratio and the half-time recovery. The lines indicate the 80% (outermost), 95%, 99%, and 99.9% (innermost) confidence interval. The maximum likelihood values are indicated by the point within the lines.

logistic regression performed for the prescribed dose, midlung point dose, and an average of the EQD2 at the midlung and prescription point. The latter term was intended to provide a more accurate approximation of the true mean lung dose for cases that use lung blocking. For treatments that used lung compensators rather than lung blocking, the EQD2 was assumed the same for the lungs and the prescription point.

To determine the values of the a/b ratio and the $T_{1/2}$, a likelihood surface plot was created (Fig. 3) to determine a 2-dimensional confidence interval (CI) at 80%, 95%, 99%, and 99.9% confidence levels for the a/b ratio and the $T_{1/2}$. The maximum likelihood, which is shown as a point in Fig. 3, was determined to be an a/b of 2.25 Gy and a $T_{1/2}$ of 0.45 hour. Both the a/b[29] and $T_{1/2}$[30] from this model are in agreement with experimental animal data. The results of the logistic regression for the prescribed dose model (P = .0004) using the maximum likelihood values for the a/b and $T_{1/2}$ are shown in Table 5. Table 5 also shows the odds ratio (OR) for the EQD2 to be 24.3 Gy^{-1} (95% CI, 7.0-84.3 Gy^{-1}). Because EQD2 is a continuous variable, the OR is the change in odds per unit (Gy) increase in EQD2. The regression model along with the study data points are shown in Fig. 4.

Table 5 Logistic regression of IPS and prescription EQD2 for $T_{1/2}$= 0.45 hour and α/β= 2.25 Gy

Coefficient: Covariate	Fit value	*P* value	OR (95% CI)
β_1 : EQD2	3.19	.0004	24.3 (7.0-84.3)
β_0 : Constant	−38.4	.0003	-

Abbreviations: CI = confidence interval; EQD2 = equivalent dose given in 2-Gy fractions; IPS = idiopathic pneumonia syndrome; OR = odds ratio.

Similar to the prescription dose EQD2 model previously discussed, a midlung dose EQD2 model and an approximated mean lung dose EQD2 model were attempted. No statistically significant relationship with IPS was found (using the same values for a/b and $T_{1/2}$ as in the prescription dose EQD2 model) for either the midlung dose EQD2 model (P = .41) or the approximate mean lung dose EQD2 model (P = .26).

The current study cannot resolve why the EQD2 related to the prescription dose resulted in a better statistical model than the EQD2 for midlung or the approximation of the true mean lung EQD2. The importance of lung dose should not be discounted despite the prescription EQD2 being a better predictor of IPS in this analysis. One possible reason the prescription dose resulted in a better model could be that the uncertainties in estimating the actual delivered lung dose were too great. Another possible reason could be that the point dose metrics (ie, midlung point dose) are simply not predictive of the real delivered dosimetry to the entire lungs. Lung dose-volume data are not available for further dosimetric analysis because volumetric dosimetric calculations were not employed in the evaluated studies. Further, the studies using lung blocking do not sufficiently describe the lung blocking methods for approximation of the lung dose-volume characteristics. In addition, there are multiple interstudy variables that are not accounted for but that may affect the IPS rates, which perhaps confound this analysis.

Dose rate is considered an important factor in TBI[31] and was an integral component of the prescription EQD2 model. The EQD2 parameter, g (see Equation 1 and 2), ranged from 0.63 to 0.95 for the modeled prescription EQD2. The trend typically shows that the longer the time to deliver the TBI dose, because of reduced dose rate, the greater the deviation of g from unity. Therefore, lower dose rates resulted in greater decrease in EQD2. To illustrate the effect of dose

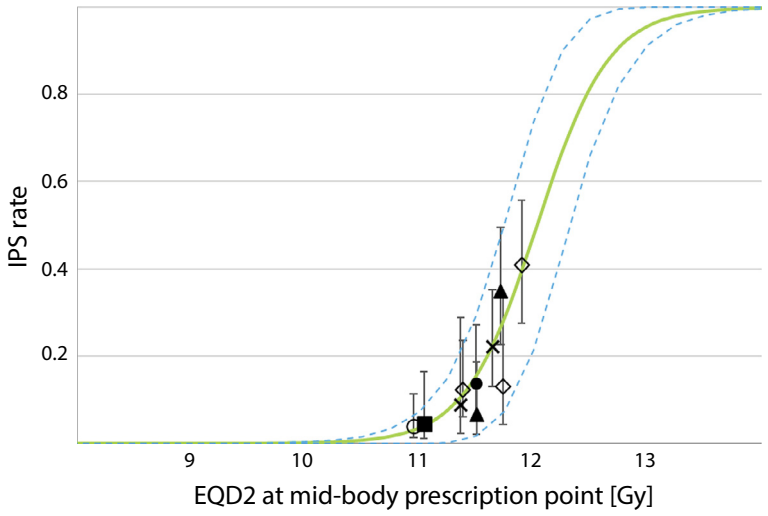

Fig. 4. Idiopathic pneumonitis syndrome versus prescription equivalent dose given in 2-Gy fractions with instantaneous dose rate correction. Regression model is shown as a solid line with the 95% confidence interval (dashed line). Individual studies are identified by the following marker types: ◇, Abugdideiri et al[24]; ▲, Gao et al[20]; ×, Kim et al[21]; •, Weshler et al[23]; ■, Spitzer et al[54]; ○, Bradley et al.[52] Studies with more than 1 data point reported multiple dose rate and/or prescribed dose cohorts. Error bars show the 95% confidence interval of the cohort.

rate consider the Kim et al[21] study, which typically used a dose per fraction of 3 Gy. The EQD2 for that study would be 23% greater than the physical dose if the EQD2 calculation did not include a dose rate component (ie, $g = 1$ in Equation 1). However, because of the low dose rates used in both cohorts of the study, the dose rate corrected prescription EQD2 was reduced to within 7% of the physical dose given at the prescription point for both cohorts. In fact, if one compares the Kim et al[21] data in Figs. 1a, 2a, and 4, in Fig. 1a it can be observed that the cohort with the greater IPS rate had the lesser physical dose, and examination of Fig. 2a shows that it had the greater dose rate. However, after the EQD2 calculation, the greater IPS rate group exhibits a greater EQD2 because of the higher dose rate.

This model suggests that for mitigation of IPS risk, further decreasing the dose rate might be an alternative to traditional lung blocking. This would be a less challenging strategy for institutions that use a lateral TBI technique, where blocking the lungs also blocks bone marrow within the sternum and thoracic vertebra. To further illustrate the role of dose rate in IPS risk mitigation, consider a common fractionation schema of 2 Gy per fraction to 12 Gy total dose. In this model a decrease in the instantaneous dose rate from 20 cGy/min (EQD2, 11.55 Gy) to 10 cGy/min (EQD2, 11.15 Gy) would reduce the predicted IPS from 18% (95% CI, 3%-33%) to 6% (95% CI, 0%-11%) manifest in the difference in the value for the parameter g in Equation 2 of 0.92 and 0.85, respectively.

The COG recently required centers to limit the cumulative midlung dose to <8.0 Gy based on a recent report of 143 patients with acute lymphoblastic leukemia undergoing transplant, with heterogeneous TBI techniques.[32] A total midlung dose of >8.0 Gy was associated with an inferior relapse-free and overall survival compared with cumulative midlung dose ≤8.0 Gy in both univariate and multivariate analyses. It is unclear how significantly IPS contributed to posttransplant morbidity and mortality, as pulmonary adverse events were only reported in 6% of enrolled patients, and the incidence of reported pulmonary adverse events was not affected by lung dose. This COG report did not analyze the influence of dose rate on the biological dose, but our data suggest it is worth exploring whether a lower dose rate can contribute to a lower IPS and mortality rate.

Association of TBI with PFT changes

PFTs are not considered accurate in the acute transplant setting and are usually not performed during or immediately after HCT. However, PFTs offer an indirect measurement of prior lung injury (from any cause) and are sometimes used to characterize late pulmonary toxicities in survivors after transplant. The studies reporting PFTs both before and after transplant or only after transplant are summarized in Table 4. Few TBI details were included in these reports. In all included series, there was at least 1 abnormal pulmonary function parameter reported during the measurement period, which ranged from 1.5 to 27 years. In a study of 89 patients who underwent PFTs pre- and posttransplant, 40% of patients had at least 1 abnormal parameter before transplantation. Posttransplant, the proportion of patients with abnormal PFT rose to 64% at a median of 8.5 years.[33] A restrictive pattern of lung injury predominated over an obstructive pattern, and most patients were asymptomatic despite abnormal PFTs. Data were conflicting in regard to the time course, with some reporting worsening of PFTs over time[33,34] and others showing a tendency toward stabilization.[7] Because these reports span several decades (1969-

2005), and many factors influence PFT testing, there is no conclusion that can be made about TBI and PFT testing, but data are included here for completeness.

Other risk factors

We were unable to determine patient age as a risk for developing IPS. Increasing age was reported as a risk factor in a 1983 report by Weiner et al[35] (relative risk for IPS of 2.2 for patients >21 years of age compared with those <21 years). However, within pediatric populations, a relationship between age and IPS has not been observed conclusively.[1,3,20,24]

Chemotherapy conditioning is an important component of HCT, with most TBI-containing regimens using cyclophosphamide. IPS has been observed in patients who have not had TBI as part of their conditioning regimen.[2,36-38] One study comparing TBI with non-TBI busulfan-based conditioning regimens identified that busulfan was associated with a significantly higher rate of IPS in both univariate and multivariate analyses.[1] A mixed adult and pediatric model of once daily fractionated TBI showed an OR between 4.5 and 5.0 for the development of IP (including IPS and viral etiologies) in patients receiving busulfan.[39] Two similar meta-analyses (but also lacking modeling and including twice per day TBI regimens) showed 1 study favoring cyclophosphamide with TBI[40] and the other not finding a significant difference.[41] None of the studies included in our IPS model used busulfan in the conditioning regimens.

These questions regarding chemotherapy regimen using busulfan resulted in the restriction of cyclophosphamide-based chemotherapy regimens for inclusion of the model. Only 2 studies that had been deemed evaluable in regard to IPS and TBI data reporting were excluded from the model based on the chemotherapy regimen.[19,42] This was an insufficient amount of data to create a model for non−cyclophosphamide-based chemotherapy regimens or to include in the current model analysis as an additional covariate. Interpretation of the current model for a non−cyclophosphamide-based chemotherapy regimen should carefully consider the toxicity profiles of the chemotherapy agents used. Although use of different chemotherapy agents may prevent the use of this model to calculate a specific IPS risk, the general influence of EQD2 (and its dependence on total dose, dose per fraction, and dose rate) may still be useful for radiation therapy clinicians in evaluation of their own TBI programs.

The development of acute GVHD has been associated with IPS.[2,35,43,44] The exact mechanism is unclear, with direct toxic effects of the chemoradiotherapy, cytokine/chemokine or endotoxin release all postulated.[44] Development of GVHD was associated with IPS in univariate analysis in 3 studies[3,24,35] included in the literature search review. One study found GVHD to remain significant on multivariate analysis.[3] Another study found a significant association between acute GVHD and pulmonary toxicity in univariate analysis, but GVHD and IPS were not correlated.[24]

IPS rates were low in the 2 trials of autologous HCT[45,46] included in Table 2 (excluded from IPS analysis). The rates of IPS were 5% and 6% in these 2 trials, which is much lower than many allogeneic trials, suggesting that the graft versus host effect and/or immune reconstitution in the latter may influence the development of IPS.

Comparison with previously reported models

A study by Sampath et al[39] consisting of both adult and pediatric data generated 3 models for predicting interstitial pneumonia (IP) using logistic regression. IP was defined to include IPS as well as viral etiologies such as cytomegalovirus but excluded bacterial sources. This study determined an a/b ratio of 2.8 Gy for IP. This a/b value is within the 99% CI for a range of $T_{1/2}$ values (Fig. 3) of the current IPS model. This model differed from ours in several important ways. First, the Sampath et al[39] analysis was only able to generate models for 1 fraction/d TBI schedules. Second, it used total lung dose and the product of the total lung dose and the lung dose per fraction (which were found to be statistically significant covariates in all 3 of their models), while we used EQD2 as previously described. It is important to note that while Sampath et al used lung dose data, our model uses prescribed dose. Third, the Sampath et al study specifically did not find lung dose rate to be a significant covariate while we did when we included dose rate at the prescription point in our model, as it was found to have an association with IPS in other studies.[20,24]

Limitations

There are many issues that may limit the present analysis, which are discussed in the following sections.

Clinical considerations

The effect of longer treatment times resulting from lower dose rates for pediatric patients may affect patient compliance, which could increase the need for patient sedation. The use of audio/visual technologies can improve patient compliance despite longer treatment times associated with lower dose rates. Additionally, the utilization of lung blocks, which typically require lung block placement and verification images, can further increase the procedure time for the patient. Future adoption of IMRT techniques may extend treatment procedure times even longer than those for low-dose-rate TBI techniques.

Dosimetric uncertainties

Systematic dosimetric analyses of different TBI techniques are lacking and are limited for many reasons. Many radiation oncology departments have independently developed a

technique for TBI delivery based on their specific linear accelerator (or cobalt unit) capabilities as well as logistics, including treatment room field size constraints and dose rate limitations.

In TBI, the dosimetric uncertainty is much greater for the lungs than other anatomic sites such as the pelvis, which is typically the location of the prescription point (this may be the origin of why the current model could only be achieved for the prescription point dose). The difficulty in determining accurate lung dose is amplified in cases that use lung blocks rather than lung compensators. In TBI, dose calculation for the lung is still often performed at a single point in midlung instead of using volumetric image sets derived from CT. Therefore, dose-volume data are not available in the published reports considering TBI.

Because dose is usually prescribed to a midplane point (usually in the pelvis), the dose deposition within the lung, if unmitigated, is higher because of reduced attenuation through the lung. Without some form of mitigation for this effect, the dose to the lung can be up to 10% to 15% greater than the prescribed dose. For TBI techniques that use either lung blocking or lung compensation to mitigate this effect, the difference in midlung point dose and actual delivered lung dose is dependent on lung block design (eg, size and fabrication technique) and placement of the block in relation to the ribcage and the mediastinum. Few reports that used lung blocking described the margin from the block edge to the lung tissue interface, typically measured from chest radiographs. This can affect the size of the lung blocks and, therefore, the actual mean lung dose.[47] For conventional TBI, it is more common to perform lung blocking in an AP convention than with a lateral technique. With the AP technique, portions of the ribs are underdosed by the lung blocks, but this can be compensated for with electron beams to the affected areas of the chest wall. Reports using lung blocking with an AP convention rarely reported whether the chest under the lung block was boosted with electron fields and, if so, the associated increase in lung dose. In general, lateral TBI techniques have also been shown to exhibit high difference between midlung dose and mean dose to the lung.[48,49] Although no studies used lung blocking with a lateral TBI technique, it would conceivably be difficult to accurately compensate underdosed bone marrow sites (eg, spine, sternum, and arms). Intensity modulated based delivery techniques have the promise to reduce lung dose for TBI while maintaining dose to stem cell sites with accurate lung dose-volume calculations. For the purposes of this analysis, it was assumed that each institution had properly verified the lung dosimetry for at least the midlung point dose. In this review, some studies used fractionated TBI regimens with lung blocking only on 1 or a few fractions to achieve a desired total midlung dose; no attempt to model the biologic implications of this method was performed. In those cases, the total midlung point dose was taken as the reported lung dose and the lung dose rate was calculated as the TBI dose rate scaled by the ratio of total midlung point dose to the prescribed dose.

A summary of the estimated uncertainty for the studies used in the IPS model is presented in Appendix E3. The accuracy in the assumed lung dose was estimated based on the description of the TBI technique(s) for each study included the modeling analysis. Additionally, the technique of delivering TBI is highly variable, as highlighted in Tables 2 and 3.

Endpoint uncertainties

The definition of IPS is variable in the evaluable literature, as shown in Table 1. Three[20,21,24] out of the total 6 studies included in the model used a definition of IPS similar to the guidelines of the American Thoracic Society.[5] Future studies should use this definition of IPS to allow better interstudy comparison by use of consistent endpoints.

Toxicity Scoring Recommendations

Using the established CTCAE for pneumonitis scoring is recommended. A recent study found grade 3 to 4 pulmonary toxicity was associated with decreased survival.[50] Pneumonitis in the presence of known infectious agents should be classified as infectious pneumonitis.

It is recommended that patients undergoing HCT have baseline PFTs before initiating the conditioning regimen (unless they cannot cooperate because of age) and have follow-up PFTs at prescribed intervals after HCT. Although PFT abnormalities after stem cell transplant are common, few patients reported symptoms of late effects (eg, shortness of breath). The COG surveillance recommendations after HCT recommend annual evaluation for pulmonary symptoms and baseline PFTs (including diffusion capacity of the lung for carbon monoxide and spirometry) and subsequently as appropriate depending on symptoms and initial findings.[51]

Data-Reporting Standards Specific to TBI

We propose the following reporting in future TBI-related IPS studies:

- Prior radiation therapy, chemotherapy, and other relevant pulmonary factors
- Use American Thoracic Society definition5 of HCT-related IPS
- Use CTCAE scoring of pneumonitis severity
- Age at diagnosis and age at TBI
- Prescription point location
- Prescribed dose-fractionation data
- Detailed dosimetric data for lung dose (ie, lung blocking or compensation techniques and margins)
  - Tissue inhomogeneity calculation assumptions
  - Dose-volume histogram of lung, if possible

- Point dose calculation methodology
- Dose rate (instantaneous and average)
- Time interval between fractions
- Testing for statistical significance of IPS with the following:
  - Chemotherapy agents used (and timing with respect to the TBI)
  - GVHD prophylaxis methods
  - Stem cell source
- Uniform late toxicity endpoints and PFT results as described previously

Future Investigations

A statistical model correlating dose-rate adjusted EQD2 of TBI prescription dose with IPS risk for allogeneic transplants using a cyclophosphamide-based chemotherapy conditioning regimen was determined. This model shows a considerable change in IPS risk for a narrow window of EQD2 (eg, 11-12 Gy). Although strategies to minimize radiation-induced IPS have generally focused on reducing the lung dose (eg, with lung blocking in traditional TBI or with advanced methods of intensity modulated TBI), this model suggests modest reduction strategies, such as reduced TBI dose rate, may be a clinically feasible strategy to effectively reduce the risk of IPS. Further clinical data can be used to test and/or refine the model. Investigations of other chemotherapy regimens (including chemotherapy-only conditioning regimens) may provide further insights into understanding the risks associated with TBI-containing regimens. The relative contribution of GVHD is another important issue for study. As CT-based planning for TBI using IMRT increases, the effect of dose rate and mean lung dose on IPS will need to be re-examined.

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