Practical Radiation Oncology® (2020) **10**, e397–e405

practical radiation oncology®
pro
www.practicalradonc.org

Clinical Investigation

Acute Respiratory Events and Dosimetry of Total Body Irradiation Patients Using In Vivo Lung Dose Monitoring and Custom Lung Block Adaptation

Julie K. Jang, MD, PhD,[a,b] Michael Reilly, PhD,[a] George Yaghmour, MD,[c] Faisal Rashid, BA,[a] and Leslie K. Ballas, MD[a,*]

[a]Department of Radiation Oncology, Norris Cancer Center, Keck School of Medicine of University of Southern California, Los Angeles, California; [b]Department of Radiation Oncology, Los Angeles County + USC Medical Center, Los Angeles, California; and [c]Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases, Norris Cancer Center, Keck School of Medicine of University of Southern California, Los Angeles, California

Received 14 November 2019; revised 26 February 2020; accepted 14 March 2020

Abstract

Purpose: Most myeloablative regimens before stem cell transplant involved total body irradiation (TBI). Pulmonary complications from TBI contribute to treatment-related mortality and toxicity. We report the rate of acute respiratory complications after TBI at our institution. In an exploratory analysis, we investigated differences in dosimetry between patients who did and did not experience respiratory complications.

Methods and Materials: In this single institution retrospective study, 49 patients received TBI from 2016 to 2018 and had dosimetry data available for analysis. Patients were prescribed 1200 cGy to be delivered over 6 fractions. Lung doses were limited using custom lung blocks. Clinical lung complications (eg, coughing and shortness of breath) were reviewed for the hospitalization period during transplant, at 4 months after transplant, and at 1 year after transplant. Supplemental oxygen use during the hospitalization period was also reported. Median anterior-posterior diameter at the umbilicus, body mass index, and lung doses were compared between patients with and without respiratory complications using a Mann-Whitney *U* test.

Results: During the hospitalization period, 14% (n = 7) of patients used supplemental oxygen administered by nasal canula and 16% (n = 8) experienced respiratory symptoms. At the 4-month follow-up, 16% (n = 8) of patients had documented respiratory symptoms. Respiratory symptoms were grade 1 to 2 except for one grade 3 attributed to infection during the hospitalization period and another grade 3 due to infection during the 4-month follow-up. At 1-year post-TBI, 4% (n = 2) of patients reported grade 1 to 2 chronic cough. Patients with respiratory complications at the 4-month follow-up had a larger umbilical anterior-posterior diameter (31.5 cm vs 26.5 cm, $P = .01$) and body mass index (34.5 kg/m^2 vs 29.7 kg/m^2, $P = .02$) than patients without respiratory complication. Respiratory complications were not associated with higher lung doses.

Meeting presentation: An abstract was presented as a poster-resentation at the 2019 ASTRO Annual Meeting in Chicago, IL.

Sources of support: The project described was supported in part by award number P30CA014089 from the National Cancer Institute, United States. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Disclosures: The authors have no conflicts of interest with the submitted work. Dr Yaghmour is a pharmaceutical board speaker for Jazz, Takeda, and Astellas pharmaceutical companies and an advisor to Jazz and Incyte.

Research data will be shared upon request to the corresponding author.

* Corresponding author: Leslie K. Ballas, MD; E-mail: lballas@med.usc.edu

https://doi.org/10.1016/j.prro.2020.03.005

Conclusions: There was no respiratory-related mortality using the individualized planning technique described here. Acute and chronic respiratory complications were minor, with the most significant intervention requiring antibiotics for respiratory infection.

Introduction

Total body irradiation (TBI) is part of the conditioning regimen for patients with hematologic malignancies undergoing hematopoietic stem cell transplant (SCT), and it is used in approximately 10% of autologous and 46% of allogeneic SCT worldwide.[1] At myeloablative doses (12-15 Gy) and in combination with chemotherapy, TBI helps to eliminate residual malignant cells, deplete host bone marrow to provide "space" for donor engraftment, and reduce rejection of donor cells. Although less intensive conditioning regimens may employ chemotherapy alone, TBI has several advantages. Unlike chemotherapy, TBI is not dependent on pharmacokinetics, can penetrate "sanctuary sites" such as testes and brain, and may eradicate target cells resistant to chemotherapy.

The more intense a myeloablative conditioning protocol is, the more likely it is to eliminate residual disease, with the caveat of causing more toxicities. Although the common acute symptoms (eg, nausea, diarrhea, erythema, fatigue, parotitis, mucositis, etc) of TBI are transient and manageable, toxic effects on entire organs can result in long-term sequelae and mortality.[2-4] Long-term conditions may include but are not limited to endocrinopathies, secondary neoplasm, and renal and pulmonary disease. The treatment-related mortality or non-relapse-related mortality has ranged between 13% and 30% over the past 2 decades.[2-4] The majority of treatment-related mortality occurs within the first 3 months after hematopoietic cell transplantation and is usually due to infection, acute lung injury, or central nervous system complications.[3]

In early series before the 1980s, pulmonary complications were the most frequent serious complications, occurring in over 50% of patients, with 63% of pulmonary complications being lethal.[5-7] The rate of pulmonary complications has decreased significantly over time, ranging from 8% to 33%, with even fewer cases being lethal.[2-4,8-11] The decreases in pulmonary complications are attributed to improvements in supportive care post-transplant, a shift toward fractionated TBI,[12,13] reduced dose rates,[14-18] and reduced lung dose.[19-21]

Lung shielding is one method of reducing lung dose, but how and to what extent this method is used varies widely among institutions. Guidelines for TBI from the American College of Radiology and American Society for Radiation Oncology do not specify how or when lung shielding should be done.[22] Guidelines from the International Lymphoma Radiation Oncology Group simply state that most centers should limit lung doses to 8 to 10 Gy and provide some of the methods used.[23] We provide the method for lung shielding used by our institution over the past 3 years and the rate of respiratory complications.

Methods and Materials

Patients

Fifty-six patients received TBI at Norris Cancer Center (Los Angeles, CA) from January 2016 through December 2018. This study was approved by the institutional review board under HS-18-00991.

Conditioning regimen

Patients were conditioned with either fludarabine for 3 consecutive days before TBI or cyclophosphamide for 2 consecutive days before TBI at the discretion of the treating hematologist. After TBI, patients received 1 of 4 regimens for acute graft versus host disease (GVHD) prophylaxis (tacrolimus and methotrexate, cyclophosphamide and tacrolimus and mycophenolate, tacrolimus and methotrexate and antithymocyte globulin, or cyclophosphamide alone).

Radiation therapy

Before radiation treatment, patient simulation began with a 2-step process. Physical anterior-posterior diameter (APD) measurements were taken in the lateral decubitus position using calipers. APD measurements of the patients' head, neck, chest, abdomen, and hips were used to generate custom Lucite compensators and Cerrobend blocks to ensure approximately 10% dose homogeneity. A previously acquired diagnostic chest computed tomography (CT) scan acquired in the supine position was used to calculate water equivalent thickness (WET). The WET was then subtracted from the patients' umbilical APD to calculate the number of Lucite compensator plates required for customized lung compensation. Similar calculations were performed for the head and neck region, although additional considerations for radiation beam off-axis uniformity were taken into account. Superflab bolus was used in the neck region to provide a higher degree of WET uniformity, and rice bags were used at the patient's lower extremities to provide compensation in this region. Patients were prescribed 1200 cGy, delivered over 6 fractions (200 cGy delivered

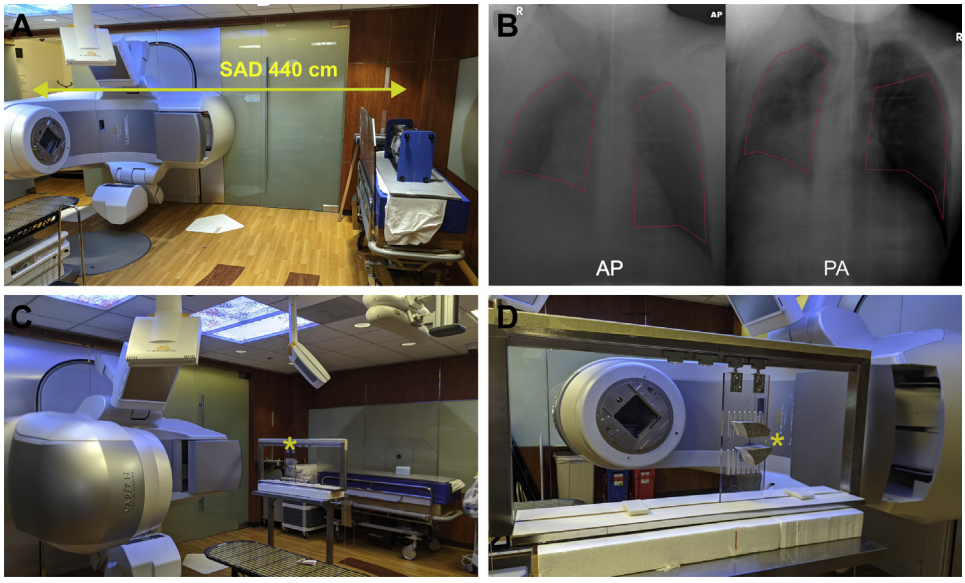

Figure 1 Total body irradiation (TBI) set-up. Patients were treated in the decubitus position with anterior-posterior/posterior-anterior (AP/PA) beams with surface-to-axis distance (SAD) of 440 cm (yellow arrow), with the beam spoiler and phantom shown on the right side of the room (A). Lung blocks were designed (red) using the AP and PA radiograph films, where we blocked the lungs below the clavicles and $\leq$5 mm medial to the chest wall (B). When used, the lung blocks (near the yellow asterisks) hung on a platform 1 meter from the beam spoiler between the beam spoiler and linear accelerator (C, D).

twice a day over 3 days). Monitor unit calculations were performed using tissue-maximum ratio for the umbilical APD. Figure 1 shows our typical set-up.

Patients were treated lying in the lateral decubitus position with anterior-posterior and posterior-anterior (AP/PA) beams. Radiation was delivered on the Varian TrueBeam System with 40 $\times$ 40 cm^2 open field, with the collimator rotation set to 45°, using 15 megavoltage (MV) photons, at 440 cm source-to-axis distance (SAD). A beam spoiler was placed 30 cm from the patient's midline. The dose rate was 200 MU/min, corresponding to a range of 8.2 to 10.2 cGy/min depending on the patients' APD.

Optically stimulated luminescence detectors (OSLDs; nanoDot^{TM} dosimeter from LANDAUER) were placed on the patient body surface at the level of the umbilicus, left lung, and right lung. MV imaging was performed at the first fraction to design a custom 5 half-value-layer Cerrobend right and left lung block (Fig 1B). During the second fraction, the custom lung blocks were positioned a meter from the beam spoiler and patient, and a subsequent MV image was taken to verify their positioning. OSLD measurements were repeated to quantify the extent of dosimetric attenuation to the lungs. The lung blocks were used in 3 of 6 fractions to maintain total lung dose between 700 to 900 cGy.

Respiratory events

Three time points were evaluated: during hospitalization for transplantation, 4 months post-TBI, and 1 year post-TBI. Respiratory events based on symptoms (ie, coughing, dyspnea on exertion, and shortness of breath) and imaging findings were evaluated retrospectively by reviewing clinicians' clinical documentation and diagnostic imaging reports during the specified period. Respiratory events were graded using the Common Terminology Criteria for Adverse Events v5.0. During the hospitalization period, we also recorded the use of supplemental oxygen as an objective surrogate marker of respiratory function.

Statistics

Correlations between measured umbilical APD, body mass index (BMI), and dosimetric measurements (monitor units, OSLD total umbilical dose, OSLD total right lung dose, OSLD total left lung dose) were evaluated using Pearson correlation analysis. As part of an exploratory analysis, we compared the umbilical APD, BMI, and lung dose among patients with respiratory sequelae to patients without respiratory sequelae using a 2-tailed Mann-Whitney U test, with $\alpha = 0.05$. The relationship between respiratory events and conditioning regimen was evaluated using a Fisher exact test, with $\alpha = 0.05$. There were not enough events of interest to allow for a multivariable analysis. Statistical analysis was done using GraphPad Prism.

Results

Respiratory outcomes

Forty-nine of 56 patients treated between January 2016 and December 2018 had data regarding lung shielding available for analysis. Table 1 includes the patient demographics for the 49 patients included in analysis. All patients had Karnofsky Performance Scores of at least 80 and had acceptable pulmonary function tests (diffusing capacity for carbon monoxide, and forced expiratory volume in 1 second, greater than 60%) before TBI. One patient had documented asthma. Patients had received a variety of chemotherapeutic agents before their conditioning regimen, the most common being the USC ALL regimen.[24] To the authors' knowledge, no patient had received busulfan or bleomycin before TBI. Patients received either fludarabine or cyclophosphamide for the conditioning regimen. If patients received fludarabine in combination with TBI for the conditioning regimen, then they received posttransplant cyclophosphamide on day 3 and day 4 after SCT for GVHD prophylaxis. The relationship between conditioning regimen and respiratory events was not statistically significant, although there was a trend toward association with supplemental oxygen use during the hospitalization period ($P = .11$).

Respiratory events are summarized in Table 2. During the hospitalization period, 8 (16%) patients experienced clinically documented lung complications (cough, shortness of breath, dyspnea on exertion, adventitious sounds on lung examination, or findings on CT chest or chest radiographs). All respiratory complications were grade 1 to 2, except for 1 patient with grade 3 adverse events due to respiratory infection confirmed by bacterial cultures. Because documentation and grading of symptoms can be subjective, we also looked at the use of supplementary oxygen during this period as an objective surrogate for respiratory complications. Before TBI, no patients used supplemental oxygen. After TBI, 7 (14%) patients used supplemental oxygen in the form of nasal cannula. No patients required intubation. The rate of clinical respiratory event or supplemental oxygen use was 22% (11 of 49).

At 4 months after TBI, 8 (16%) patients had clinically documented respiratory complications presenting as cough, shortness of breath, or dyspnea on exertion. One of these cases was attributed to asthma exacerbation in a patient with a preexisting history of asthma. All respiratory symptoms were grade 1 to 2, except for 1 patient who required intravenous antibiotics for suspected pneumonia. Three of the 8 patients had suspected GVHD of the lungs based on symptoms and imaging studies and were treated with oral steroids. One patient died during this period due to gastrointestinal-related toxicity. From the bone marrow biopsies done at 100 days posttransplant, 2 patients had relapsed. Another 2 patients had minimal residual disease.

We have follow-up data for 45 patients at 1-year posttransplant. Of the remaining 4 patients, 1 died of gastrointestinal-related toxicity as previously described, 1 died of septic shock, and 2 were lost to follow-up owing to a change in providers. Of the 45 patients with follow-up, 2 (4%) reported grade 2 chronic cough, corresponding to findings on thoracic imaging. They were suspected to have GVHD of the lungs and their coughing improved after a course of steroids. Of the 49 patients included in this study, 5 patients had relapsed within a year of their transplant.

Table 1 Patient demographics and measurements from dosimetry

	Total patients, n = 49
Number of females	21 (43%)
Median age at time of TBI (range)	40 (19-61)
BMI in kg/m^2 (range)	30.4 (19.9-47.1)
Number with disease (%)	
ALL	37 (75%)
B-ALL	32 (65%)
T-ALL	5 (10%)
T-cell lymphoma	2 (4%)
AML	9 (18%)
Myeloid dysplastic syndrome	1 (2%)
Number receiving donor type (%)	
Matched unrelated donor	10 (20%)
Haploidentical relative	39 (80%)
Number receiving conditioning regimen (%)	
Cyclophosphamide	29 (59%)
Fludarabine	20 (41%)
Number receiving acute GVHD prophylaxis regimen (%)	
Tacrolimus, methotrexate	23 (47%)
Cyclophosphamide, tacrolimus, mycophenolate	21 (43%)
Tacrolimus, methotrexate, antithymocyte globulin	3 (6%)
Cyclophosphamide	2 (4%)
Median APD in cm (range)	27 (20-39.5)
Median dose rate in cGy/min (range)	9.5 (8.2-10.2)
Median total body dose in cGy (range)	1212 (1104-1302)
Median total right lung dose in cGy (range)	780 (432-898)
Median total left lung dose in cGy (range)	765 (384-873)

Abbreviations: ALL = acute lymphoblastic lymphoma; AML = acute myeloid leukemia; APD = anterior-posterior diameter; BMI = body mass index; GVHD = graft versus host disease; TBI = total body irradiation.

Table 2 Rate of respiratory complications

	Hospitalization period (n = 49)	120-days post-TBI (n = 49)	1-year post-TBI (n = 45)
Patients with supplemental O_2 use	7 (14%)	-	-
Patients with respiratory sequelae	8 (16%)	8 (16%)	2 (4%)
Grade 1-2	7 (14%)	7 (14%)	2 (4%)
Cough	5	4	2
Shortness of breath/dyspnea	1	3	0
Lung infection	0	1	0
Findings on imaging	3	4	2
Grade 3	1 (2%)	1 (2%)	0 (0%)
Lung infection	1	1	0

Abbreviation: TBI = total body irradiation.

Relationship between umbilical anterior-posterior diameter and respiratory complications

As previously described, umbilical APD measurements were used to calculate the monitor units required to deliver 200 cGy per fraction (100 cGy per field), resulting in a strong positive correlation between umbilical APD and monitor units ($r = 0.9987$; $r^2 = 0.9974$; $P < .0001$; Fig 2A). Not surprisingly, umbilical APD also correlated with patients' BMI ($r = 0.8496$; $r^2 = 0.7219$; $P < .0001$; Fig 2B). Although monitor units were expected to vary with the umbilical APD, the expected total dose should have been approximately 1200 cGy for each patient and vary independently with the umbilical APD. Contrary to those expectations, the umbilical APD was also positively correlated with total dose at the umbilicus ($r = 0.6459$; $r^2 = 0.4172$; $P < .0001$; Fig 2C). The idea that larger or more obese patients might be receiving more radiation at their umbilicus is supported by the correlation of BMI with umbilical dose ($r = 0.4339$; $r^2 = 0.1883$; $P = .002$; Fig 2D). Neither umbilical APD nor BMI correlated with total dose received at either lung (Fig 2E,F).

In an exploratory analysis, we queried whether patients with respiratory events had different dosimetry measurements from patients who did not have respiratory events. Data are summarized in Table 3. In the hospitalization period, patients who used supplemental oxygen did not have statistically different umbilical APD, BMI, or lung dose compared with those who did not use supplemental oxygen. There was also no statistical difference between those who did or did not have clinical respiratory events.

At the 4-month follow-up, patients who experienced respiratory symptoms had significantly different median umbilical APD (31.6 cm; interquartile range, IQR, 28.4-34.9 cm) than patients who did not have events (26.5 cm; IQR, 23.3-29.3; $P = .01$; Fig 3A). Similarly, patients who had respiratory symptoms during this period had higher median BMI (34.5 kg/m^2; IQR, 31.0-36.5) than patients without symptoms (29.7 kg/m^2; IQR, 25.6-33.3; $P = .02$; Fig 3B). Although respiratory symptoms were associated with larger umbilical APD and BMI, they were not associated with higher lung doses, possibly as a result of individualized lung compensation. There were too few patients with respiratory adverse events at the 1-year follow-up for analysis.

Table 3 shows a statistically significant lower right lung dose for patients with respiratory symptoms at the 4-month follow-up, which conflicts with what is known about pulmonary toxicity and radiation dose. However, this difference between 729 cGy (IQR, 632-770) among symptomatic patients and 786 cGy (IQR, 739-810) among asymptomatic patients is small and unlikely to be clinically significant. The APD differences and BMI differences, however, are of both clinical and statistical significance. The median and interquartile ranges of BMI among symptomatic patients are within the obese category, while the median BMI of asymptomatic patients is classified as overweight but not obese.

Discussion

The primary objective of this study was to report incidence of respiratory complications after TBI using our institution's method of lung shielding. During the hospitalization period, 16% of patients had new respiratory signs or symptoms. The same rates were seen 4 months after TBI, although not necessarily in the same patients. The rate of respiratory complication increases to 22% when adding the use of supplemental oxygen as a respiratory event. These rates are within the range of rates reported in contemporary studies of myeloablative TBI.[2-4,8-11] However, an important difference is that our study included grade 1 and 2 respiratory events, whereas prior

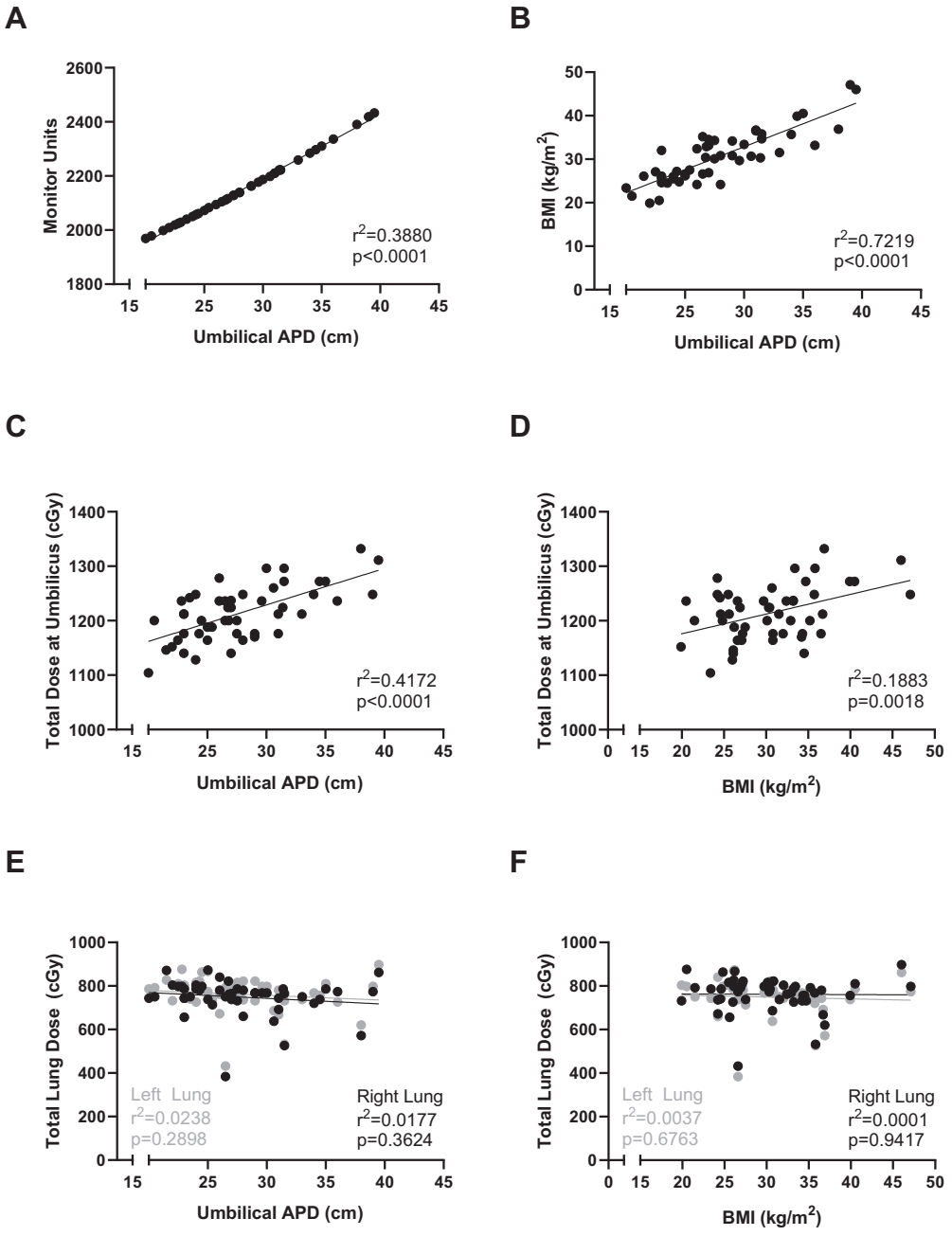

Figure 2 Correlation of dosimetry measurements. Correlation of umbilical anterior-posterior diameter (APD) in cm (ie, patient thickness) with monitor units (A) and body mass index (BMI) (B). Correlation of total dose at the umbilicus with umbilical APD (C) and BMI (D). Correlation of total lung dose with umbilical APD (E) and BMI (F). Total doses at the umbilicus, right lung, and left lung were obtained from the optically stimulated luminescence detectors (OSLD).

studies only included grade 3 to 5 events or reported specific respiratory events such as pneumonitis. Our rationale for being more inclusive was to reduce bias so that coding of events was less subject to our interpretation. The overreporting of events in the acute period is likely reflected in the relatively few respiratory sequelae (4%) we observed a year after TBI.

Direct comparisons to other studies are also difficult owing to differences in the length of the follow-up period. We were interested in the acute period, whereas most studies included patients with long-term follow-up. In an older study reporting acute side effects, myeloablative TBI (12-13.5 Gy delivered in twice daily fractions) resulted in at least grade 3 pulmonary toxicity in 14% of patients within 100 days of their transplant. Details of the set-up and lung dose were not included nor were they a focus of their study.[3] In a more recent study evaluating a similar time interval (90 days posttransplantation), the rate

Table 3 Mann-Whitney *U* analysis comparing median umbilical APD, BMI, and lung dose between patients who did or did not experience respiratory events

	Umbilical APD (cm)		BMI (kg/m^2)		Right lung dose (cGy)		Left lung dose (cGy)	
Hospitalization period, supplemental O_2 use								
Yes	28.0	$P = .76$	27.1	$P = .93$	768	$P = .64$	768	$P = .65$
No	26.9		30.6		783		764	
Hospitalization period, clinical events								
Yes	27.3	$P > .99$	33.3	$P = .64$	777	$P = .62$	759	$P = .63$
No	27.0		30.3		780		765	
120-days post-TBI, clinical events								
Yes	31.6	$P = .01$	34.5	$P = .02$	729	$P = .02$	748	$P = .16$
No	26.5		29.7		786		768	

Abbreviations: APD = anterior-posterior diameter; BMI = body mass index.

of grade 3 to 5 pulmonary toxicity was 33%. They delivered radiation with opposed laterals, with total dose 13.5 Gy delivered in 1.5 Gy fractions twice a day, with dose rates of 15 to 20 cGy/min and with lungs attenuated to a median dose of 10 Gy using the arms and brass compensators.[9] Taking into consideration that all our patients received pre- or post-transplant cyclophosphamide, which can add additional lung toxicity, our lower rates of pulmonary toxicity may be due to the lower lung doses or reduced dose rates.

The American Society for Radiation Oncology and International Lymphoma Radiation Oncology Group guidelines describe opposed fields as a common technique for TBI delivery,[22,23] which we used in the current study. Other radiation techniques for myeloablation exist and are being evaluated for their ability to reduce toxicity without compromising remission. TBI using volumetric-modulated arc therapy (VMAT) may offer better dose homogeneity and greater ability to spare organs at risk than conventional techniques. In 2 reports on the dosimetry and delivery of myeloablative TBI using VMAT, no acute respiratory toxicities were observed among 37 patients total.[25,26] However, these studies focused on treatment delivery, and little information is provided on how toxicity was assessed. In a small study reporting on the use of helical tomotherapy for TBI delivery, 2 of 11 patients experienced grade 1 or 2 pulmonary complications in the form of pleural effusions.[27] These pilot studies warrant further investigation and longer follow-up.

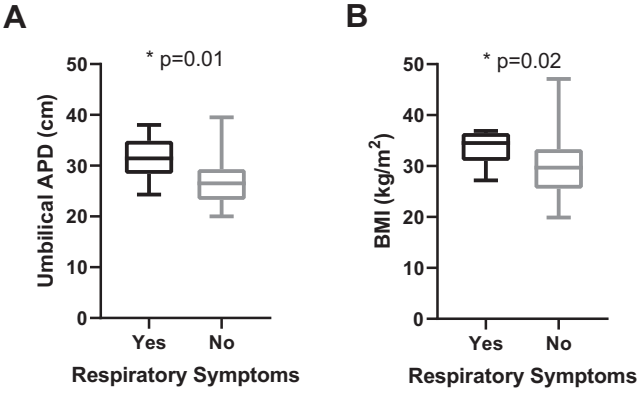

Figure 3 Boxplot of umbilical anterior-posterior diameter (APD) (A) and body mass index (BMI) (B) among patients with and without respiratory symptoms at 4 months posttotal body irradiation (TBI).

Helical tomotherapy and VMAT also allow for more targeted forms of TBI, such as total marrow irradiation (TMI) and total marrow and lymphoid irradiation (TMLI). In TMI and TMLI, the treatment volume would encompass the entire bony skeleton, with possible coverage of lymphoid tissue and/or protected sites such as brain and testes. Several early phase trials report their use in relapse/refractory multiple myeloma and acute leukemia, with mean lung dose generally below 8 Gy.[28-32] In a recent report of toxicity from 3 TMI/TMLI trials, only 0.7% (1 of 142) of patients developed radiation pneumonitis, which they defined as at least grade 3 pneumonitis not attributable to infection, GVHD, or disease progression. Another 45 of their patients developed pulmonary symptoms attributed to infection.[33] Several problems arise when restricting the endpoint to radiation pneumonitis. Determining the etiology of lung disease can be difficult and inaccurate. Second, the exclusion of lung disease from infection, GVHD, or disease progression assumes that the etiologies are mutually exclusive—that radiation pneumonitis and GVHD could not have occurred together or that radiation pneumonitis did not contribute to infection susceptibility. The study likely underestimates pulmonary toxicity. Nonetheless, the authors reported good safety profiles. Their 2-year cumulative incidence of pulmonary toxicity from infection or radiation pneumonitis was 22.7%,[33] which is comparable to the data presented in this study.

A secondary objective of this study was to find differences in the characteristics between patients who did and did not experience respiratory toxicity. In an exploratory analysis, we were surprised by the results shown in Figure 2C, showing that patients with larger

umbilical APD (ie, greater thickness) received greater total dose as measured from their umbilical OSLD. We hypothesize that the correlation between APD and umbilicus dose is the result of using physical APD measurement for monitor unit calculation. This contrasts with the right and left lung dose measurements where Lucite compensators and lung blocks are designed based on a thickness measurement that is corrected for density from a patient's chest CT scan. We expect that if the physical APDs were similarly "distance-corrected" based on CT measurement, then patients with larger APD would better correlate with the tissue-maximum-ratio monitor unit dosimetry calculation.

Patients with respiratory toxicity had a higher umbilical APD. Because patients with larger umbilical APD had higher dose at the umbilicus, we were initially concerned that the relationship between umbilical APD and toxicity might be due to increased radiation dose. However, umbilical APD was not correlated with lung dose, and patients with respiratory toxicity did not have higher lung doses. In our cohort, lung doses were kept below 9 Gy, with relatively little variation from the median. We hypothesize that the larger umbilical APD is related to respiratory toxicity due to obesity-related pulmonary complications. The higher BMI in these patients supports our hypothesis. Although it is well known that obesity is related to pulmonary complications in the nontransplant setting, it is not well characterized in the stem cell transplant setting. A retrospective study from Japan of 3935 patients showed that pre-transplantation BMI was associated with increased risk of acute GVHD and infection.[34] A subsequent meta-analysis also concluded that obese recipients have increased risk of acute GVHD.[35] To the authors' knowledge, this is the first study associating obesity with respiratory complications in the post-TBI setting. Our study provides a possible "threshold" BMI to use in future studies exploring the relationship between obesity and post-TBI respiratory events. Furthermore, it would be interesting to know in future studies if umbilical APD predicted respiratory events better than BMI, as it may better reflect visceral obesity.[36-38]

Our study has several limitations in addition to the general limitations of retrospective studies. There were relatively few events of interest, which prevented any multivariable analysis. Our outcome of interest, other than supplemental oxygen use, is also subject to biased reporting of the documenting physician. Routine post-TBI pulmonary function tests were not done, which would have provided objective quantifiable outcomes for analysis.

Conclusions

We describe our institutional method of myeloablative TBI and report respiratory complications during hospitalization, at 4 months post-TBI, and at 1-year post-TBI. Our events were mostly grade 1 to 2 events, with no respiratory-related deaths. Among patients who experienced respiratory toxicity, they had higher umbilical APD and BMI, suggesting that obese patients are at higher risk for pulmonary complications after TBI.

References

1. Hong S, Barker C, Klein JP, et al. Trends in utilization of total body irradiation (TBI) prior to hematopoietic cell transplantation (HCT) worldwide. *Biol Blood Marrow Transplant*. 2012;18:S336-S337.
2. Lohr F, Wenz F, Schraube P, et al. Lethal pulmonary toxicity after autologous bone marrow transplantation/peripheral blood stem cell transplantation for hematological malignancies. *Radiother Oncol*. 1998;48:45-51.
3. Diaconescu R, Flowers CR, Storer B, et al. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. *Blood*. 2004;104:1550-1558.
4. DEF F, Grapulin L, Musio D, et al. Treatment complications and long-term outcomes of total body irradiation in patients with acute lymphoblastic leukemia: A single institute experience. *Anticancer Res*. 2016;36:4859-4864.
5. Thomas ED, Buckner CD, Banaji M, et al. One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. *Blood*. 1977;49:511-533.
6. Neiman PE, Reeves W, Ray G, et al. A prospective analysis interstitial pneumonia and opportunistic viral infection among recipients of allogeneic bone marrow grafts. *J Infect Dis*. 1977;136:754-767.
7. Keane TJ, Van Dyk J, Rider WD. Idiopathic interstitial pneumonia following bone marrow transplantation: The relationship with total body irradiation. *Int J Radiat Oncol Biol Phys*. 1981;7:1365-1370.
8. Chiang Y, Tsai CH, Kuo SH, et al. Reduced incidence of interstitial pneumonitis after allogeneic hematopoietic stem cell transplantation using a modified technique of total body irradiation. *Sci Rep*. 2016;6:36730.
9. Kelsey CR, Horwitz ME, Chino JP, et al. Severe pulmonary toxicity after myeloablative conditioning using total body irradiation: An assessment of risk factors. *Int J Radiat Oncol Biol Phys*. 2011;81:812-818.
10. Schneider RA, Schultze J, Jensen JM, Hebbinghaus D, Galalae R, Kimmig BN. 20 years of experience in static intensity-modulated total-body irradiation and lung toxicity. Results in 257 consecutive patients. *Strahlenther Onkol*. 2007;183:545-551.
11. Schneider RA, Schultze J, Jensen JM, Hebbinghaus D, Galalae RM. Long-term outcome after static intensity-modulated total body radiotherapy using compensators stratified by pediatric and adult cohorts. *Int J Radiat Oncol Biol Phys*. 2008;70:194-202.
12. Deeg HJ, Sullivan KM, Buckner CD, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission: Toxicity and long-term follow-up of patients conditioned with single dose or fractionated total body irradiation. *Bone Marrow Transplant*. 1986;1:151-157.
13. Socie G, Devergie A, Girinsky T, et al. Influence of the fractionation of total body irradiation on complications and relapse rate for chronic myelogenous leukemia. The Groupe d'Etude des greffes de moelle osseuse (GEGMO). *Int J Radiat Oncol Biol Phys*. 1991;20:397-404.
14. Travis EL, Peters LJ, McNeill J, Thames HD Jr, Karolis C. Effect of dose-rate on total body irradiation: Lethality and pathologic findings. *Radiother Oncol*. 1985;4:341-351.

15. Weiner RS, Bortin MM, Gale RP, et al. Interstitial pneumonitis after bone marrow transplantation. Assessment of risk factors. *Ann Intern Med*. 1986;104:168-175.
16. Kim DY, Kim IH, Yoon SS, Kang HJ, Shin HY, Kang HC. Effect of dose rate on pulmonary toxicity in patients with hematolymphoid malignancies undergoing total body irradiation. *Radiat Oncol*. 2018; 13:180.
17. Gao RW, Weisdorf DJ, DeFor TE, Ehler E, Dusenbery KE. Influence of total body irradiation dose rate on idiopathic pneumonia syndrome in acute leukemia patients undergoing allogeneic hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys*. 2019;103:180-189.
18. Abugideiri M, Nanda RH, Butker C, et al. Factors influencing pulmonary toxicity in children undergoing allogeneic hematopoietic stem cell transplantation in the setting of total body irradiation-based myeloablative conditioning. *Int J Radiat Oncol Biol Phys*. 2016;94: 349-359.
19. Della Volpe A, Ferreri AJ, Annaloro C, et al. Lethal pulmonary complications significantly correlate with individually assessed mean lung dose in patients with hematologic malignancies treated with total body irradiation. *Int J Radiat Oncol Biol Phys*. 2002;52:483-488.
20. Labar B, Bogdanic V, Nemet D, et al. Total body irradiation with or without lung shielding for allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1992;9:343-347.
21. Esiashvili N, Lu X, Ulin K, et al. Higher reported lung dose received during total body irradiation for allogeneic hematopoietic stem cell transplantation in children with acute lymphoblastic leukemia is associated with inferior survival: A report from the Children's Oncology Group. *Int J Radiat Oncol Biol Phys*. 2019;104:513-521.
22. Wolden SL, Rabinovitch RA, Bittner NH, et al. American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) practice guideline for the performance of total body irradiation (TBI). *Am J Clin Oncol*. 2013;36:97-101.
23. Wong JYC, Filippi AR, Dabaja BS, Yahalom J, Specht L. Total body irradiation: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys*. 2018;101:521-529.
24. Douer D, Aldoss I, Lunning M, et al. Pharmacokinetics-based integration of multiple doses of intravenous pegaspargase in a pediatric regimen for adults with newly diagnosed acute lymphoblastic leukemia. *J Clin Oncol*. 2014;32:905-911.
25. Springer A, Hammer J, Winkler E, et al. Total body irradiation with volumetric modulated arc therapy: Dosimetric data and first clinical experience. *Radiat Oncol*. 2016;11:46.
26. Tas B, Durmus IF, Okumus A, et al. Total-body irradiation using linac-based volumetric modulated arc therapy: Its clinical accuracy, feasibility and reliability. *Radiother Oncol*. 2018;129:527-533.
27. Sarradin V, Simon L, Huynh A, Gilhodes J, Filleron T, Izar F. Total body irradiation using Helical Tomotherapy((R)): Treatment technique, dosimetric results and initial clinical experience. *Cancer Radiother*. 2018;22:17-24.
28. Wong JY, Rosenthal J, Liu A, Schultheiss T, Forman S, Somlo G. Image-guided total-marrow irradiation using helical tomotherapy in patients with multiple myeloma and acute leukemia undergoing hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys*. 2009;73:273-279.
29. Somlo G, Spielberger R, Frankel P, et al. Total marrow irradiation: A new ablative regimen as part of tandem autologous stem cell transplantation for patients with multiple myeloma. *Clin Cancer Res*. 2011;17:174-182.
30. Wong JY, Forman S, Somlo G, et al. Dose escalation of total marrow irradiation with concurrent chemotherapy in patients with advanced acute leukemia undergoing allogeneic hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys*. 2013;85:148-156.
31. Patel P, Aydogan B, Koshy M, et al. Combination of linear accelerator-based intensity-modulated total marrow irradiation and myeloablative fludarabine/busulfan: A phase I study. *Biol Blood Marrow Transplant*. 2014;20:2034-2041.
32. Patel P, Oh AL, Koshy M, et al. A phase 1 trial of autologous stem cell transplantation conditioned with melphalan 200 mg/m(2) and total marrow irradiation (TMI) in patients with relapsed/refractory multiple myeloma. *Leuk Lymphoma*. 2018;59:1666-1671.
33.. Shinde A, Yang D, Frankel P, et al. Radiation related toxicities using organ sparing total marrow irradiation transplant conditioning regimens. *Int J Radiat Oncol Biol Phys*. 2019;105:1025-1033.
34. Fuji S, Kim SW, Yoshimura K, et al. Possible association between obesity and posttransplantation complications including infectious diseases and acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2009;15:73-82.
35. Nakao M, Chihara D, Niimi A, et al. Impact of being overweight on outcomes of hematopoietic SCT: A meta-analysis. *Bone Marrow Transplant*. 2014;49:66-72.
36. Sugerman H, Windsor A, Bessos M, Wolfe L. Intra-abdominal pressure, sagittal abdominal diameter and obesity comorbidity. *J Intern Med*. 1997;241:71-79.
37. Smith DA, Ness EM, Herbert R, et al. Abdominal diameter index: A more powerful anthropometric measure for prevalent coronary heart disease risk in adult males. *Diabetes Obes Metab*. 2005;7:370-380.
38. de Souza NC, de Oliveira EP. Sagittal abdominal diameter shows better correlation with cardiovascular risk factors than waist circumference and BMI. *J Diabetes Metab Disord*. 2013;12:41.