Bone Marrow Transplantation (2007) 40, 573–578

www.nature.com/bmt

ORIGINAL ARTICLE

Pulmonary function following total body irradiation (with or without lung shielding) and allogeneic peripheral blood stem cell transplant

BP Soule[1], NL Simone[2], BN Savani[3], H Ning[2], PS Albert[4], AJ Barrett[3] and AK Singh[2]

[1]*Radiation Biology Branch, National Cancer Institute, NIH, Bethesda, MD, USA;* [2]*Radiation Oncology Branch, National Cancer Institute, NIH, Bethesda, MD, USA;* [3]*National Heart Lung Blood Institute, NIH, Bethesda, MD, USA and* [4]*Biometric Research Branch, National Cancer Institute, NIH, Bethesda, MD, USA*

Our purpose was to determine if total body irradiation (TBI) with lung dose reduction protects against subsequent radiation-induced deterioration in pulmonary function. Between July 1997 and August 2004, 181 consecutive patients with hematologic malignancies received fractionated TBI before allogeneic peripheral blood stem cell transplant. The first 89 patients were treated to a total dose of 13.6 Gy. Thereafter, total body dose was decreased to 12 Gy with lung dose reduction to 9 or 6 Gy. All patients underwent pulmonary function test evaluation before treatment, 90 days post-treatment, then annually. Median follow-up was 24.0 months. Eighty-nine patients were treated with lung shielding, and 92 without. At 1-year post transplant, there was a small but significant difference in lung volume measurements between patients with lung shielding and those without. This was not observed at the 2-year time point. When stratified by good ($>100\%$ predicted) or poor ($\leqslant 100\%$ predicted) baseline lung function, patients with poor function demonstrated protection at 1 year with lung shielding, while those with good initial lung function did not. TBI with or without lung dose reduction has a small but statistically significant effect on pulmonary function measured at 1 year but not 2 years post irradiation.

Bone Marrow Transplantation (2007) **40,** 573–578; doi:10.1038/sj.bmt.1705771; published online 16 July 2007
Keywords: pulmonary function; total body radiation; stem-cell transplant; lung shielding

Introduction

Total body irradiation (TBI) is important in the preparation of patients for bone marrow or peripheral blood stem cell transplant (PBSCT) in the treatment of various malignancies.[1–9] Although regimens employing chemotherapy alone may be effective, evidence suggests that TBI improves post transplant survival compared to the use of chemotherapy alone.[10–12] The addition of TBI has several advantages including the absence of cross-resistance of host marrow cells to different chemotherapeutic agents and the ability to sterilize disease in 'sanctuary' sites which are not easily penetrated by chemotherapeutic agents.[13,14]

Pulmonary toxicity may result from TBI as an acute or a late complication.[15–22] Studies have shown that the severity depends on both dose rate and total dose administered.[22–26] Several strategies have emerged to address this complication, including increasing the fractionation schedule to decrease the radiation dose administered at any one time[26–34] and reducing the lung dose directly by utilizing lung shielding.[17,28] Several studies have described an association between lung dose reduction and pulmonary-related mortality and overall survival.[35–38] Previous analysis of this cohort demonstrated that stratification by pretreatment pulmonary function testing (PFT) identified patients for whom lung shielding resulted in a 20% 1-year survival benefit.[35]

In this study, we investigated whether, in addition to improving survival, TBI with lung dose reduction protects against radiation-induced, post treatment deterioration in lung function as measured by standard PFTs.

Methods

Study group

Between July 1997 and August 2004, 181 consecutive patients with hematologic malignancies received a T cell-depleted PBSCT from an HLA-matched sibling. These patients were enrolled in one of five National Heart, Lung and Blood Institute's (NHLBI) institutional review board-approved protocols (97-H-0099, 99-H-0046, 02-H-0111, 03-H-0192, 04-H-0112). This is a report of all patients enrolled on these protocols with adequate follow-up for meaningful analysis.

Conditioning regimen

Three pretransplant conditioning regimens were employed in consecutive time periods to prepare the patient for PBSCT. Regimen A was administered from April 1997 to

Correspondence: Dr AK Singh, Radiation Oncology Branch, National Cancer Institute, 10 Center Drive, Building 10-CRC, Room B2-3500 (MSC 1642), Bethesda, MD 20892, USA.
E-mail: singan@mail.nih.gov
Received 6 September 2006; revised 29 May 2007; accepted 4 June 2007; published online 16 July 2007

December 2001 ($n = 89$) consisted of TBI administered to a dose of 13.6 Gy with no lung shielding, resulting in a lung dose of more than 13.6 Gy to the lungs due to tissue density, and cyclophosphamide 120 mg/kg. Regimen B was administered from February 2002 to May 2003 ($n = 35$) and comprised TBI to a dose of 12 Gy with lung shielding, cyclophosphamide 120 mg/kg and fludarabine 125 mg/m^2. In this regimen, lung shielding was customized for each patient such that the total prescribed lung dose was reduced to 9 Gy. Regimen C consisted of 12 Gy of TBI with lung shielding (6 Gy prescribed lung dose), cyclophosphamide 120 mg/kg and fludarabine 125 mg/m^2 from June 2003 to August 2004 ($n = 57$). Patients who had lung shielding received a radiation boost dose to the mediastinum to bring the total dose to 12 Gy to ensure adequate ablation of sternal and mediastinal myeloid tissues.

Radiation technique

During regimen A, TBI was administered using lateral fields without any lung shielding. The patient was placed 4 m from the treatment machine with the collimator fully open. After treatment of one lateral field, the patient was turned to allow treatment of the opposed field. Dose was calculated using the midpoint of the separation distance measured from the patient's hips in the sitting position. Patients received 1.7 Gy twice daily for 4 days. Daily fractions were 6 h apart. Dose rate at midplane was approximately 0.12 Gy/min. A compensator was used to minimize dose gradients produced by different tissue thicknesses in the head-and-neck region and torso. Dose was verified using diodes placed on the patient's skin in the lateral neck, axilla, hip, midthigh and midcalf.

Regimen B lowered the total prescribed dose from 13.6 to 12 Gy, given in 1.5 Gy twice-daily fractions. Initially, under regimen B, the cumulative lung dose was limited to 9 Gy. The lung dose was further reduced by regimen C to 6 Gy.

Lung dose was selectively reduced by the addition of a 50% partial transmission lung block for the lateral fields. Computed tomography (CT) simulation with the patient in the treatment position was used to localize the apex and inferior border of the lung. Dose was verified with diodes placed as above. With this technique, the mediastinum, vertebral bodies and humeral heads under the partial transmission lung block also only received 50% of the dose from the lateral fields. Dose to these structures was supplemented by anterior and posterior boost fields to bring the dose to 12 Gy. These boost fields were given at 1-m treatment distance with a match at the superior and inferior field borders of the lateral field lung block. Five half-value layer lung blocks minimized additional dose to the lungs.

For both regimens B and C, the dose rate at midplane was approximately 0.12 Gy/min for the lateral fields and 2 Gy/min for the anterior and posterior boost fields. Dose volume histogram analysis verified that 50% of the lung received approximately 50% of the total dose. Approximately 15% of both the left and right lungs received 100% of the dose. With the previously described lateral fields-only method (regimen A), more than 90% of the lung received at least 100% of the prescribed dose.

Peripheral blood stem cell transplant regimen

Patients were enrolled in one of five NHLBI protocols for PBSCT. In the first protocol, patients received a T cell-depleted granulocyte colony-stimulating factor-mobilized PBSCT by using the Ceprate selection system (CellPro, Bothell, WA, USA). Subsequent protocols used an Isolex 300 cell separator, as described previously.[39] CD34 cells were positively selected using anti-CD34 beads, and residual T cells were removed with a cocktail of anti-CD2, -CD6 and -CD7 antibody-coated beads. The CD34 cell dose ranged from 2.45 to 15.90×10^6 cells/kg recipient weight (median, 5.0×10^6/kg); the T-cell dose was 0.2–1.0×10^5 CD3 cells/kg. In the absence of GVHD or unless molecular remission was documented in chronic myeloid leukemia, T cells were added back on days 45 and 100, or day 60. Cyclosporine (CSA) was administered to prevent transplant rejection and dose varied according to protocol. All patients started CSA either on day 44 (if T cells were added back on day 45) or on day 59 (if T cells were added back on day 60), and it was continued until at least day 130 (or longer if chronic GVHD occurred). Standard prophylaxis against infection included fluconazole through day 100, cotrimoxazole for 6 months after transplantation, and weekly surveillance for cytomegalovirus antigenemia, as described previously.[39,40] Acute GVHD was managed with high-dose steroids. Steroid-refractory patients who showed no improvement after 7 days of treatment received combined treatment with antitumor necrosis factor (infliximab) and anti-CD25 (daclizumab) monoclonal antibodies, as described previously.

Pulmonary function testing

Baseline PFTs were obtained for all patients 5–21 days before PBSCT. Ventilatory capacity was measured by forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), the FEV_1/FVC ratio and peak expiratory flow. Lung volume measurements (by helium dilution) included vital capacity (VC), total lung capacity, residual volume and the residual volume/total lung capacity ratio. Diffusion capacity for carbon monoxide (DL_{CO}) was determined by using a carbon monoxide single-breath technique with correction for hemoglobin concentration.[41] PFTs were expressed as a percentage of the predicted values in healthy controls with corresponding age, sex and smoking habits. Eligibility criteria for enrollment into protocols included $DL_{CO} > 60\%$ of predicted. For this analysis, FEV_1 and DL_{CO} limits of 100% of predicted were used to identify at-risk patients with a combination of abnormal inspiratory function and gas diffusion, respectively.

Statistical analysis

In the first analysis, the average preirradiation value for each PFT parameter was compared to the value at 1 year after transplantation for both the lung shielding and no-lung shielding groups. Patients were then stratified by preradiation baseline PFT values into good (>100% expected) and poor ($\leqslant$100% expected) groups. This analysis was also performed on the subgroup of patients who had 2 years of follow-up.

In a second analysis, an estimate of linear change of each PFT parameter over time (in units of change in % predicted

per year) was estimated by fitting a least-squares regression line to each patient's available data and examining the slope of the resulting line. This gives an estimate of the rate of change in pulmonary function over time and, unlike in the previous analyses, all longitudinal follow-up measures are used. The distribution of these estimated slopes for the good and poor baseline PFT groups was then compared. This analysis was performed on the group of patients for whom 1 year or greater PFT data were available.

Results

In total, 89 patients were treated without lung shielding and 92 were treated with lung shielding. Median follow-up was 24.0 months (range 0.26–119.3 months). One hundred and nine patients had 1 year of follow-up; 91 patients had 2 years of follow-up. Patient demographics are listed in Table 1 and are similar between groups.

Table 1 Patient demographics

	Lung shielding (n = 92)	*No lung shielding (n = 89)*	P-*values*
% Male	50	58	0.30
Age (years), median (range)	32 (10–55)	38 (10–56)	0.006
% Positive smoking history	3	11	0.05
Presenting disease (%)			
AML	30	27	
ALL	26	8	
CML	26	43	
CLL	—	3	
MDS	15	15	
Other	1	7	
% Prior busulfan use	2	5	0.11
Prescribed total body radiation dose (cGy), mean	1200	1360	<0.001
Prescribed lung radiation dose (cGy), mean (range)	714 (600–900)	1360 (1360–1360)	<0.001

Abbreviation: MDS = myelodysplastic syndrome.
P-values for continuous variables are based on a two-sided Wilcoxon rank-sum test. *P*-values for frequencies are based on two-sided Fisher's exact tests.

In the initial analysis, the effect of lung shielding on changes in PFT values at 1 and 2 years (Table 2) for all patients was assessed. Positive values indicate an improvement in the pulmonary function parameter while negative values signify a decline. There was a small, but statistically significant, difference between the FEV_1 and VC values for all patients at the 1-year follow-up point. There was no difference in DL_{CO} measurements. There was no statistically significant difference in the change in lung function between those patients with lung shielding and those with no lung shielding measured at 2 years post transplant. Furthermore, there was no difference in PFT measurements between the two lung shielding radiation doses (9 versus 6 Gy).

When patients were stratified by good or poor lung function as defined in the methods section, those with poor lung function demonstrated a benefit from lung shielding at 1 year, while those with good preirradiation lung function had a much smaller and statistically nonsignificant benefit of lung shielding on lung function (Table 3). This was also observed when poor lung function was defined as $\leqslant 80\%$ predicted (data not shown). We did not observe this differential lung shielding effect when patients were stratified by good and poor lung function at 2 years (data not shown).

The rate of change in lung function over time was compared for all patients with at least 1 year of follow-up using a least-squares regression as described above (Table 4). This analysis revealed no difference in the rate of change in lung function over time between those patients with lung shielding and those without lung shielding. Once again, this was the case when looking at all patients together and when patients were stratified by good or poor lung function.

Discussion

This study shows that TBI with lung dose reduction may result in small improvements in long-term, post transplant

Table 2 Total change in PFT values

	1-year follow-up			*2-year follow-up*		
	Lung shielding	*No lung shielding*	P-*values*	*Lung shielding*	*No lung shielding*	P-*values*
FEV_1	2.5 (−3.0 to 8.3) $n = 40$	−5.5 (−16.8 to 2.8) $n = 38$	0.004	−2.0 (−6.0 to 4.0) $n = 33$	−2.0 (−12.8 to 1.8) $n = 30$	0.41
DL_{CO}	−15.0 (−28.5 to −5.0) $n = 39$	−17.5 (−29.0 to −4.8) $n = 36$	0.61	−18.0 (−32.3 to 2.0) $n = 32$	−15.0 (−25.8 to −7.8) $n = 30$	0.78
VC	2.0 (−3.3 to 6.5) $n = 40$	−3.0 (−14.0 to 1.0) $n = 38$	0.009	−2.0 (−6.0 to 4.0) $n = 33$	−2.0 (−12.8 to 17.5) $n = 30$	0.34

Abbreviations: DL_{CO} = diffusion capacity for carbon monoxide; FEV_1 = forced expiratory volume in the first second; PFT = pulmonary function testing; VC = vital capacity.
The median change in PFT measurements from pretransplant to 1 year and 2 years after transplant is compared between lung shielding groups for all patients. Values represent the median change in PFT values, measured as % predicted, with range from 1st to 3rd quartile. The FEV_1 and VC are significantly different between those patients with lung shielding and those with no lung shielding at the 1-year time point. There are no significant differences between the groups at the 2-year time point. *P*-values are based on a two-sided Wilcoxon rank-sum test.

Table 3 Total change in PFT values at 1 year by preirradiation function

	Good preirradiation PFTs			*Poor preirradiation PFTs*		
	Lung shielding	*No lung shielding*	P-*values*	*Lung shielding*	*No lung shielding*	P-*values*
FEV_1	0 (−4.0 to 5.0) $n=21$	−3.5 (−17.5 to 1.3) $n=20$	0.07	7.0 (−2.5 to 13.0) $n=19$	−8.0 (−15.8 to 3.8) $N=18$	0.03
DL_{CO}	−28.5 (−36.8 to −18.3) $n=18$	−28.0 (−38.0 to −26.0) $n=13$	0.60	−6.0 (−15.0 to 6.0) $n=21$	−10.0 (−22.0 to −2.0) $n=23$	0.30
VC	−2.0 (−9.3 to 1.25) $n=14$	−3.0 (−16.0 to 1.0) $n=13$	0.42	3.5 (−0 to 8.8) $n=26$	−3.0 (−14.0 to 1.0) $n=25$	0.007

Abbreviations: DL_{CO} = diffusion capacity for carbon monoxide; FEV_1 = forced expiratory volume in the first second; PFT = pulmonary function testing; VC = vital capacity.
The median change in PFT measurements from pretransplant to 1 year after transplant is compared between lung shielding groups after stratification by good and poor preirradiation PFT measurements. Values represent the median change in PFT values, measured as % predicted, with range from 1st to 3rd quartile. There was a statistically significant difference in the change in lung function between those patients with lung shielding and those with no lung shielding for patients with poor ($\leqslant$100% predicted) preirradiation PFTs. There were no significant differences in lung function for patients with good (>100% predicted) preirradiation PFTs. *P*-values are based on a two-sided Wilcoxon rank-sum test.

Table 4 Rate of change of PFT values during 1-year follow-up

	All patients			*Good pre-irradiation PFTs*			*Poor pre-irradiation PFTs*		
	Lung shielding	*No lung shielding*	P-*values*	*Lung shielding*	*No lung shielding*	P-*values*	*Lung shielding*	*No lung shielding*	P-*values*
FEV_1	−0.40 (−2.8 to 2.9) $n=46$	−0.11 (−4.6 to 1.7) $n=49$	0.33	−0.78 (−5.6 to 2.1) $n=24$	−0.14 (−4.8 to 2.1) $n=22$	0.90	1.2 (−1.0 to 5.4) $n=22$	−0.11 (−4.3 to 0.9) $n=22$	0.08
DL_{CO}	−3.7 (−7.9 to 0.8) n = 46	−3.3 (−9.2 to −0.2) n = 44	0.64	−6.5 (−16.8 to −4.6) n = 18	−6.5 (−10.5 to −2.9) n = 17	0.78	−1.0 (−4.9 to 2.0) n = 27	−2.4 (−6.9 to 0.51) n = 26	0.40
VC	0.98 (−2.9 to 2.7) $n=46$	0.05 (−2.4 to 2.2) $n=44$	0.41	−1.4 (−7.30 to 1.4) $n=16$	−0.08 (−6.1 to 1.6) $n=15$	0.86	1.8 (−1.1 to 4.7) $n=30$	−0.02 (−1.7 to 2.2) $n=29$	0.19

Abbreviations: DL_{CO} = diffusion capacity for carbon monoxide; FEV_1 = forced expiratory volume in the first second; PFT = pulmonary function testing; VC = vital capacity.
The median rate of change per year (range from 1st to 3rd quartile) in PFT parameter measurements (% predicted value) as determined by least-squares regression from pretransplant to 1 year after transplant, is compared between lung shielding groups for all patients, and stratified by good (>100% predicted) and poor ($\leqslant$100% predicted) preirradiation PFT values. There was no statistically significant difference in the rate of change in lung function between those patients with lung shielding and those with no lung shielding. *P*-values are based on a two-sided Wilcoxon rank-sum test.

pulmonary function, especially for patients with poor pretransplant PFT values. Although these findings are statistically significant, they are not likely to be clinically significant and do not fully explain our previous finding that lung dose reduction improves survival of transplant patients with initial FEV_1 and DL_{CO} less than 100% of predicted.[35]

Lung dose reduction was attempted by Molls *et al.*[17] who found that a dose of 9.3 Gy at high dose rate can result in interstitial pneumonitis in up to 50% of treated patients. Labar *et al.*[28] randomized 64 patients with leukemia to receive TBI with or without lung dose reduction The probability of interstitial pneumonitis decreased from 15 to 5% with lung dose reduction, and there was no impact on the rate of relapse. Although the results were not statistically significant, they do show a trend toward protection against interstitial pneumonitis with lung shielding. Weshler *et al.*[42] randomized 44 patients to receive TBI to a total dose of 12 Gy with or without lung dose reduction to 6 Gy. The rate of interstitial pneumonitis in the unshielded group was 26% versus none in the shielded group.[42]

Similarly, in a prior analysis we found reduced pulmonary mortality (10 vs 3%, $P=0.08$) with lung dose reduced TBI.[35] The current analysis shows that TBI has a minimal impact on long-term, post transplant pulmonary function, which is not likely to be clinically significant. There is a small, but statistically significant benefit to lung dose reduction at 1 year, which is seen in patients with poor ($\leqslant$100% predicted) preirradiation PFT values but not good (>100% predicted) preirradiation PFT values. This finding is in agreement with prior studies that have

reported that TBI does not result in significant deterioration of long-term lung function despite causing severe acute morbidity in the form of interstitial pneumonitis, and even death.[37,43,44]

In a study of patients with osteogenic sarcoma who received adjuvant therapy consisting of whole-lung irradiation (with the heart shielded), Ellis *et al*.[43] found decreased in FEV_1, VC and DL_{CO} during the first 6–12 months after irradiation. These values returned to baseline, however, during the second year following irradiation and remained at baseline throughout the remainder of the follow-up period.[43] Gore *et al*.[44] also found that while pulmonary function declined initially, it recovered to baseline levels at approximately 1 year and remained stable 2 years post-irradiation Radiation dose to the lungs was identified as one factor that delayed or impaired recovery of pulmonary function. Carlson *et al*.,[37] in a study of over 1200 patients, also found that the major risk factor for pulmonary complications was lung dose but that ventilatory dysfunction following TBI was usually mild and had no clinical significance. In our recent study of long-term PFT after allogeneic stem cell transplantation, we found no difference in PFT between reduced-intensity (non-radiated) patients and those getting TBI after median follow-up of 7.5 years (range 5–13 years).[45]

Conclusion

TBI plays an important role in conditioning regimens for bone marrow transplant and PBSCT. Decreasing the radiation dose to the lung can decrease pulmonary-related mortality. TBI, with or without lung shielding, has minimal effect on PFTs at 1 and 2 years post-irradiation. The small improvement in post transplant PFTs with lung dose reduction regimens is of little clinical significance. Therefore, lung dose reduction should be employed primarily as a means to decrease mortality in high-risk patients and not to prevent long-term deterioration in pulmonary function.

Acknowledgements

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

References

1 Shim BY, Lee MA, Byun JH, Roh SY, Song CW, Park JN *et al*. High dose chemotherapy and autologous stem cell transplantation for poor risk and recurrent non-Hodgkin's lymphoma: a single-center experience of 50 patients. *Korean J Intern Med* 2004; **19**: 114–120.
2 Reimer P, Schertlin T, Rudiger T, Geissinger E, Roth S, Kunzmann V *et al*. Myeloablative radiochemotherapy followed by autologous peripheral blood stem cell transplantation as first-line therapy in peripheral T-cell lymphomas: first results of a prospective multicenter study. *Hematol J* 2004; **5**: 304–311.
3 Kang HJ, Shin HY, Choi HS, Han KS, Ahn HS. Autologous peripheral blood stem cell transplantation with BCVAC conditioning in childhood acute myeloid leukemia. *Bone Marrow Transplant* 2004; **33**: 471–476.
4 Russell-Jones R, Child F, Olavarria E, Whittaker S, Spittle M, Apperley J. Autologous peripheral blood stem cell transplantation in tumor-stage mycosis fungoides: predictors of disease-free survival. *Ann NY Acad Sci* 2001; **941**: 147–154.
5 Varterasian M, Janakiraman N, Karanes C, Abella E, Uberti J, Dragovic J *et al*. Transplantation in patients with multiple myeloma: a multicenter comparative analysis of peripheral blood stem cell and allogeneic transplant. *Am J Clin Oncol* 1997; **20**: 462–466.
6 Giralt SA, LeMaistre CF, Vriesendorp HM, Andersson BS, Dimopoulos M, Gajewski J *et al*. Etoposide, cyclophosphamide, total-body irradiation, and allogeneic bone marrow transplantation for hematologic malignancies. *J Clin Oncol* 1994; **12**: 1923–1930.
7 Thomas ED. Total body irradiation regimens for marrow grafting. *Int J Radiat Oncol Biol Phys* 1990; **19**: 1285–1288.
8 Advisory Committee of the International Bone Marrow Transplant Registry. Report from the International Bone Marrow Transplant Registry. *Bone Marrow Transplant* 1989; **4**: 221–228.
9 McAfee SL, Powell SN, Colby C, Spitzer TR. Dose-escalated total body irradiation and autologous stem cell transplantation for refractory hematologic malignancy. *Int J Radiat Oncol Biol Phys* 2002; **53**: 151–156.
10 Blaise D, Maraninchi D, Archimbaud E, Reiffers J, Devergie A, Jouet JP *et al*. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-cytoxan versus cytoxan-total body irradiation as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. *Blood* 1992; **79**: 2578–2582.
11 Dusenbery KE, Steinbuch M, McGlave PB, Ramsay NK, Blazar BR, Neglia JP *et al*. Autologous bone marrow transplantation in acute myeloid leukemia: the University of Minnesota experience. *Int J Radiat Oncol Biol Phys* 1996; **36**: 335–343.
12 Ringden O, Ruutu T, Remberger M, Nikoskelainen J, Volin L, Vindelov L *et al*. A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: a report from the Nordic Bone Marrow Transplantation Group. *Blood* 1994; **83**: 2723–2730.
13 Boutard P, Reman O, Lemerle S, Guihard J. A relapse in the eye of acute lymphoblastic leukemia. *Ann Pediatr (Paris)* 1989; **36**: 267–268.
14 Inoue T, Ikeda H, Yamazaki H, Tang JT, Song C, Teshima T *et al*. Role of total body irradiation as based on the comparison of preparation regimens for allogeneic bone marrow transplantation for acute leukemia in first complete remission. *Strahlenther Onkol* 1993; **169**: 250–255.
15 Shank B. The balancing act: pneumonitis vs relapse in cytoreductive regimens containing total body irradiation. *Int J Radiat Oncol Biol Phys* 1996; **36**: 261–262.
16 Soubani AO, Miller KB, Hassoun PM. Pulmonary complications of bone marrow transplantation. *Chest* 1996; **109**: 1066–1077.
17 Molls M, Budach V, Bamberg M. Total body irradiation: the lung as critical organ. *Strahlenther Onkol* 1986; **162**: 226–232.
18 Cardozo BL, Zoetelief H, van Bekkum DW, Zurcher C, Hagenbeek A. Lung damage following bone marrow transplantation: I. The contribution of irradiation. *Int J Radiat Oncol Biol Phys* 1985; **11**: 907–914.
19 Thomas O, Mahe M, Campion L, Bourdin S, Milpied N, Brunet G *et al*. Long-term complications of total body

irradiation in adults. *Int J Radiat Oncol Biol Phys* 2001; **49**: 125–131.
20 Malicki J, Skrobala A, Kosicka G, Wachowiak J. The efficacy and reliability of lung protection during total body irradiation of patients with disseminated malignancies. *Neoplasma* 2005; **52**: 325–329.
21 Hirabayashi N, Goto S, Ishii M, Yuge M, Mitsuma A, Noda N. Busulfan, cyclophosphamide and total body irradiation as conditioning for allogeneic bone marrow transplantation for acute and chronic myeloid leukemia. *Bone Marrow Transplant* 1998; **21**: 1079–1083.
22 Beyzadeoglu M, Oysul K, Dirican B, Arpaci F, Balkan A, Surenkok S *et al*. Effect of dose-rate and lung dose in total body irradiation on interstitial pneumonitis after bone marrow transplantation. *Tohoku J Exp Med* 2004; **202**: 255–263.
23 Theuws JC, Kwa SL, Wagenaar AC, Seppenwoolde Y, Boersma LJ, Damen EM *et al*. Prediction of overall pulmonary function loss in relation to the 3-D dose distribution for patients with breast cancer and malignant lymphoma. *Radiother Oncol* 1998; **49**: 233–243.
24 Della Volpe A, Ferreri AJ, Annaloro C, Mangili P, Rosso A, Calandrino R *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.
25 Theuws JC, Kwa SL, Wagenaar AC, Boersma LJ, Damen EM, Muller SH *et al*. Dose–effect relations for early local pulmonary injury after irradiation for malignant lymphoma and breast cancer. *Radiother Oncol* 1998; **48**: 33–43.
26 Lohr F, Wenz F, Schraube P, Flentje M, Haas R, Zierhut D *et al*. Lethal pulmonary toxicity after autologous bone marrow transplantation/peripheral blood stem cell transplantation for hematological malignancies. *Radiother Oncol* 1998; **48**: 45–51.
27 Gopal R, Ha CS, Tucker SL, Khouri IF, Giralt SA, Gajewski JL *et al*. Comparison of two total body irradiation fractionation regimens with respect to acute and late pulmonary toxicity. *Cancer* 2001; **92**: 1949–1958.
28 Labar B, Bogdanic V, Nemet D, Mrsic M, Vrtar M, Grgic-Markulin L *et al*. Total body irradiation with or without lung shielding for allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1992; **9**: 343–347.
29 Vriesendorp HM, Chu H, Ochran TG, Besa PC, Champlin RE. Radiobiology of total body radiation. *Bone Marrow Transplant* 1994; **14** (Suppl 4): S4–S8.
30 Tait RC, Burnett AK, Robertson AG, McNee S, Riyami BM, Carter R *et al*. Subclinical pulmonary function defects following autologous and allogeneic bone marrow transplantation: relationship to total body irradiation and graft-versus-host disease. *Int J Radiat Oncol Biol Phys* 1991; **20**: 1219–1227.
31 Socie G, Devergie A, Girinsky T, Reiffers J, Vernant JP, Le Bourgeois JP *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.
32 Bearman SI, Appelbaum FR, Buckner CD, Petersen FB, Fisher LD, Clift RA *et al*. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol* 1988; **6**: 1562–1568.
33 Shank B, Chu FC, Dinsmore R, Kapoor N, Kirkpatrick D, Teitelbaum H *et al*. Hyperfractionated total body irradiation for bone marrow transplantation. Results in seventy leukemia patients with allogeneic transplants. *Int J Radiat Oncol Biol Phys* 1983; **9**: 1607–1611.
34 Latini P, Aristei C, Aversa F, Checcaglini F, Maranzano E, Raymondi C *et al*. Lung damage following bone marrow transplantation after hyperfractionated total body irradiation. *Radiother Oncol* 1991; **22**: 127–132.
35 Singh AK, Karimpour SE, Savani BN, Guion P, Hope AJ, Mansueti JR *et al*. Pretransplant pulmonary function tests predict risk of mortality following fractionated total body irradiation and allogenic peripheral blood stem cell transplant. *Int J Radiat Oncol Biol Phys* 2006; **66**: 520–527.
36 Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. *Chest* 1992; **101**: 1257–1264.
37 Carlson K, Backlund L, Smedmyr B, Oberg G, Simonsson B. Pulmonary function and complications subsequent to autologous bone marrow transplantation. *Bone Marrow Transplant* 1994; **14**: 805–811.
38 Chien JW, Maris MB, Sandmaier BM, Maloney DG, Storb RF, Clark JG. Comparison of lung function after myeloablative and 2 Gy of total body irradiation-based regimens for hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2005; **11**: 288–296.
39 Solomon SR, Nakamura R, Read EJ, Leitman SF, Carter C, Childs R *et al*. Cyclosporine is required to prevent severe acute GVHD following T-cell-depleted peripheral blood stem cell transplantation. *Bone Marrow Transplant* 2003; **31**: 783–788.
40 Nakamura R, Battiwalla M, Solomon S, Follmann D, Chakrabarti S, Cortez K *et al*. Persisting posttransplantation cytomegalovirus antigenemia correlates with poor lymphocyte proliferation to cytomegalovirus antigen and predicts for increased late relapse and treatment failure. *Biol Blood Marrow Transplant* 2004; **10**: 49–57.
41 Cotes J. *Lung Function, Assessment and Application in Medicine*, 5th edn. Blackwell Scientific Publications: Cambridge, MA, 1993.
42 Weshler Z, Breuer R, Or R, Naparstek E, Pfeffer MR, Lowental E *et al*. Interstitial pneumonitis after total body irradiation: effect of partial lung shielding. *Br J Haematol* 1990; **74**: 61–64.
43 Ellis ER, Marcus Jr RB, Cicale MJ, Springfield DS, Bova FJ, Graham-Pole J *et al*. Pulmonary function tests after whole-lung irradiation and doxorubicin in patients with osteogenic sarcoma. *J Clin Oncol* 1992; **10**: 459–463.
44 Gore EM, Lawton CA, Ash RC, Lipchik RJ. Pulmonary function changes in long-term survivors of bone marrow transplantation. *Int J Radiat Oncol Biol Phys* 1996; **36**: 67–75.
45 Savani BN, Montero A, Srinivasan R, Singh A, Shenoy A, Mielke S *et al*. Chronic GVHD and pre-transplant abnormalities in pulmonary function are the main determinants predicting worsening pulmonary function in long term survivors after stem cell transplantation. *Biol Blood Marrow Transplant* 2006; **12**: 1261–1269.