Advances in Radiation Oncology (2021) 6, 100723

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Adverse Effects of Total Body Irradiation: A Two-Decade, Single Institution Analysis

Richard Pearlman, MD,[a,*] Renee Hanna, BS,[b] Jay Burmeister, PhD,[c,d,*] Judith Abrams, PhD,[d] and Michael Dominello, DO[d]

[a]*Detroit Medical Center, Detroit, Michigan;* [b]*Michigan State University College of Human Medicine, Lansing, Michigan;* [c]*Wayne State University, Detroit, Michigan;* [d]*Karmanos Cancer Institute, Detroit, Michigan*

Received May 5, 2020; revised April 26, 2021; accepted May 7, 2021

Abstract

Purpose: Several adverse effects have been reported in the literature associated with total body irradiation (TBI). Reports of the adverse effects of TBI have been primarily drawn from single-institution retrospective analyses. We report, to our knowledge, one of the largest cohorts of patients treated with TBI using multiple preparative chemotherapy and radiation regimens.

Methods and Materials: A retrospective chart review was performed for all 705 patients treated with TBI at our institution from 1995 to 2017. Based on availability of TBI records, 622 patients (88%) had sufficient evaluable documentation for analysis. Patients received 1 of 4 conditioning regimens: busulfan-fludarabine, 2 Gy (BUFLU); fludarabine-melphalan, 2 Gy (FLUMEL); cyclophosphamide, 12 Gy fractionated (CY); or etoposide, 12 Gy fractionated (VP16). Individual patients were evaluated for 13 specific recognized adverse effects based on the Common Terminology Criteria for Adverse Events, version 5.0.

Results: Mucositis (grade 3) was the most common serious adverse effect and occurred most frequently in the group receiving the VP16 12 Gy regimen (40% vs less than 14% in each of the other groups). Serious febrile neutropenia (grade 3-5) was less frequent (24%) among patients receiving CY than among those receiving the other conditioning regimens (more than 38% in each of the other groups). The incidence of serious lung infection was less common (5%) in patients receiving CY than in those receiving VP16 (18%). There was a higher frequency of grade 3-5 diarrhea among those receiving FLUMEL (5%) and VP16 (4%) than in the other groups (<3%) ($P = .034$). Otherwise, there were no detectable differences in serious toxicity by regimen for the 13 adverse effects reviewed. Only 2 secondary malignancies were reported, and both were in the BUFLU group. Cataract formation occurred in approximately 16% of patients overall, and the rates were similar across regimens. Median time to cataract formation was 1 to 4 years across regimens, with cataracts occurring earlier in the 2-Gy regimens. The overall rate of grade ≥3 pneumonitis was approximately 2% across the entire cohort.

Conclusions: Our nearly 20-year TBI experience showed relatively low rates of radiation-related toxicities. However, cataracts were common with a relatively short onset time.

Introduction

Total body irradiation (TBI) has played an integral role in the stem cell transplantation process for the past several decades. It is commonly used as part of the pretransplant regimen for patients with acute myeloid leukemia, acute lymphocytic leukemia, and other

Sources of support: This work had no specific funding.
Disclosures: none.
*Corresponding author: Richard Pearlman, MD; E-mail: gm1107@wayne.edu

https://doi.org/10.1016/j.adro.2021.100723

hematopoietic malignancies.[1,2] As part of the preparative regimen for hematopoietic stem cell transplantation, TBI plays multiple roles. Radiation has the potential to treat sanctuary sites that are poorly penetrated by chemotherapy, such as the central nervous system. It also has an immunosuppressive effect, which contributes to the prevention of graft rejection. Another distinct advantage of TBI is that its efficacy is not affected by chemotherapy resistance.[1-3] TBI can be performed using multiple dose and fractionation schedules ranging from 2 to 15 Gy.[2] Myeloablative and nonmyeloablative regimens, both of which use decreased radiation and chemotherapy doses particularly for elderly and frail patients, have been used.[1] In addition to multiple potential radiation regimens, TBI can be combined with several different chemotherapeutic agents as part of a preparative transplant regimen.[2,3]

Although TBI has proven advantageous, it has been associated with both early and late adverse effects. Potential acute toxicities that have been described include reversible alopecia, veno-occlusive disease, nausea, diarrhea, skin erythema, and oral mucositis.[4,5] Late effects that have been reported in the literature include endocrine disorders, cardiovascular disease, interstitial pneumonitis and fibrosis, nephrotoxicity, secondary malignancy, decreased fertility, cataract formation, and osteoporosis.[4-8] In children, growth failure and neuropsychological sequelae have also been described.[6]

As a high-volume stem cell transplant center, our institution has routinely performed TBI for several decades. The purpose of this study was to characterize the early and late effects of TBI and various preparative regimens in a large patient cohort.

Methods and Materials

Records of all 705 patients treated with TBI at our institution from 1995 to 2017 were reviewed. Patients were excluded from analysis if treatment records pertaining to TBI administration were unavailable (electronic medical record keeping was initiated in the year 2000; primarily, patients from 1995-1998 did not have readily available records). A retrospective review of 622 patients who had sufficient evaluable documentation for analysis was performed. Eighteen pediatric patients were included in the cohort. Patients were treated with 1 of 4 preparative regimens as decided by the transplant team: busulfan-fludarabine, 2 Gy (BUFLU); fludarabine-melphalan, 2 Gy (FLUMEL); cyclophosphamide, 12 Gy fractionated (CY); or etoposide, 12 Gy fractionated (VP16). These regimens are listed in Table 1. Each individual patient was evaluated for 13 specific recognized adverse effects based on the Common Terminology Criteria for Adverse Events, version 5.0 (dermatitis, alopecia, febrile neutropenia, lung infection, pneumonitis, oral mucositis, nausea, diarrhea, acute respiratory distress syndrome (ARDS), cataracts, noninfective cystitis, secondary malignancy, and pulmonary fibrosis).[9]

Early adverse effects were classified as those occurring soon after TBI and included nausea, diarrhea, dermatitis, alopecia, neutropenia, and oral mucositis. Pneumonitis was considered a subacute late effect and was defined as pneumonitis of infectious or idiopathic origin occurring within 6 months of TBI. Late effects were defined as occurring more than 90 days after TBI and included cataracts, secondary malignancy, and pulmonary fibrosis. Secondary malignancies were attributed to TBI if they possessed a solid component and differed from the patient's original diagnosis, as these were thought more likely to be related to radiation rather than recurrence of initial disease. Pathologic confirmation was required to diagnose a secondary malignancy.

Radiation treatment

Radiation was delivered using a dedicated Co-60 unit (dose rate, 2 cGy/min to 15 cGy/min). Patients were treated with either 2 Gy in a single fraction without lung blocking or 12 Gy delivered in 6 to 8 total fractions twice daily, prescribed to the midplane. Data for lung blocking was available only from 2007 onward owing to changes in record keeping. The eyes were not shielded during any treatments because of concerns for increased risk of recurrence.

Statistical analysis

Regimens were compared for severity of adverse effects using χ^2 tests for differences between two proportions and Cuzick's test for differences in proportions when there were more than two ordered groups. A Kruskal-Wallis test was used to test differences between regimens in continuous characteristics. Differences in time-to-event distributions were described using the Kaplan-Meier method and assessed with the log-rank test. Follow-up time was described using the reverse Kaplan-Meier method. Baseline demographic data were described using proportions, and continuous variables were reported using medians with interquartile ranges. Potential risk factors for the formation of cataracts were investigated using univariable and multivariable analysis. Univariable analysis was performed using a log-rank test, and multivariable testing was performed using a Cox proportional hazards model. No adjustment for multiple testing was made. This study was conducted under an approved institutional review board of Karmanos Cancer Institute/Wayne State University protocol.

Table 1 Patient demographic and baseline characteristics by TBI regimen

Characteristic	BUFLU, No. (%)(n = 330)	FLUMEL, No. (%)(n = 85)	CY, No. (%)(n = 112)	VP16, No. (%)(n = 95)	Total, No. (%)(N = 622)	*P* value
Diagnosis						
ALL	3 (0.9)	25 (29.4)	20 (17.9)	79 (83.2)	127 (20.4)	<.001
AML	162 (49.1)	28 (32.9)	5 (4.5)	6 (6.3)	201 (32.3)	
MDS	97 (29.4)	7 (8.2)	0 (0.0)	1 (1.1)	105 (16.9)	
NHL	19 (5.8)	15 (17.6)	77 (68.8)	7 (7.4)	118 (19.0)	
Other	49 (14.8)	10 (11.8)	10 (8.9)	2 (2.1)	71 (11.4)	
Transplant						
Allograft related	112 (33.9)	32 (37.6)	32 (28.6)	33 (34.7)	209 (33.6)	<.001
Allograft unrelated	218 (66.1)	53 (62.4)	33 (29.5)	60 (63.2)	364 (58.5)	
Autograft	0 (0.0)	0 (0.0)	47 (42.0)	2 (2.1)	49 (7.9)	
Age at BMT, median (IQR), y	63 (58-67)	57 (47-62)	46.5 (36-54)	30 (23-43)	57.5 (43-64)	<.001
Sex						
Female	146 (44.2)	29 (34.1)	41 (36.6)	39 (41.1)	255 (41.0)	.25
Male	183 (55.5)	56 (65.9)	71 (63.4)	56 (58.9)	366 (58.8)	
Missing	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	
Race						
African American	20 (6.1)	5 (5.9)	18 (16.1)	11 (11.6)	54 (8.7)	<.001
Caucasian	302 (91.5)	62 (72.9)	90 (80.4)	76 (80.0)	530 (85.2)	
Other	8 (2.4)	18 (21.2)	4 (3.6)	8 (8.4)	38 (6.1)	
Smoker						
No	135 (40.9)	41 (48.2)	61 (54.5)	57 (60.0)	294 (47.3)	.002
Yes	195 (59.1)	44 (51.8)	50 (44.6)	36 (37.9)	325 (52.3)	
Missing	0 (0.0)	0 (0.0)	1 (0.9)	2 (2.1)	3 (0.5)	
BMI (kg/m^2), median (IQR)	27 (24-32)	28 (23-31)	27 (24-31)	26 (22-31)	27 (24-32)	.41
Admission KPS, median (IQR)	70 (70-80)	70 (70-80)	90 (90-100)	80 (70-90)	80 (70-90)	<.001
TBI year, median (IQR)	2013 (2010-2015)	2011 (2009-2015)	2002 (2000-2006)	2009 (2007-2012)	2011 (2006-2014)	<.001

Abbreviations: ALL = acute lymphocytic leukemia; AML = acute myelocytic leukemia; BMI = body mass index; BMT = bone marrow transplant; BUFLU = busulfan-fludarabine; CY = cyclophosphamide; FLUMEL = fludarabine-melphalan; IQR = interquartile range; KPS = Karnofsky performance score; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; TBI, total body irradiation; VP16 = etoposide.

Results

Demographics

The median follow-up for survivors in the cohort was 60 months (95% CI, 51-63 months). There were large differences in some demographic characteristics among the 4 treatment regimens (Table 1). These differences likely reflect clinical decision making based on patient factors such as overall health and diagnosis. Patients receiving nonmyeloablative regimens tended to be older and were more likely to have a diagnosis of acute myeloid leukemia compared with patients receiving myeloablative regimens, which predominantly comprised younger patients with a diagnosis of acute lymphocytic leukemia or non-Hodgkin lymphoma. More patients with myelodysplastic syndrome were treated with the BUFLU regimen than with the other regimens. There was a male predominance across the entire cohort; however, the proportion of males was similar among regimens. Patients receiving the cyclophosphamide- or etoposide-based regimens had a lower rate of smoking compared with older patients undergoing the 2-Gy regimens. Median Karnofsky performance scores also tended to be higher among the cyclophosphamide and etoposide-based regimens, which is likely related to the younger median age of these cohorts.

Survival and follow-up

There were substantial differences in follow-up and survival data between the 4 regimens (Tables 2 and 3). The longest median follow-up time by treatment regimen was 129 months. The shortest median follow-up time was 47 months, in the BUFLU group. Overall, the median follow-up time was 60 months. Median overall survival ranged from 17 months in those receiving FLUMEL to 69 months in those receiving CY. There were no large or statistically significant differences in overall survival or progression-free survival by treatment regimen or diagnosis. Survival was primarily based on information available in the medical record.

Early adverse effects

Dermatitis occurred once within the entire cohort (Table 4). However, alopecia was relatively common in all treatment groups, with a rate of approximately 20%. Febrile neutropenia was another common adverse effect within the cohort. Grade 3 febrile neutropenia was predominant and ranged from 23% to 41.2%. Grade 3 to 5 neutropenia occurred in approximately 37% of patients (Table 5). The CY 12-Gy group experienced the lowest rate of grade 3 or higher febrile neutropenia (P = .010). Lung infections were also relatively common, with grade 2 infections occurring in 24% of patients overall. FLUMEL 2 Gy (14%) and VP16 12 Gy (18%) showed higher rates of grade 3 to 5 lung infections compared with BUFLU 2 Gy (8%) and CY 12 Gy (5%) regimens (P = .003). Moderate-severe nausea was more common in patients receiving FLUMEL, although the differences between groups was modest and not statistically significant. Similarly, diarrhea was more common in those on the FLUMEL regimen (grade 2 diarrhea occurred in 41%; P = .05) than among those on other regimens (BUFLU 2

Table 2 Follow-up time and survival by treatment regimen

Outcome	BUFLU (n = 330)	FLUMEL (n = 85)	CY (n = 112)	VP16 (n = 95)	Total (N = 622)
Follow-up time, median (95% CI), mo	47 (42-54)	53 (36-85)	129 (66-146)	69 (50-91)	60 (51-63)
Progression-free survival, median (95% CI), mo*	9 (6-15)	7 (5-13)	13 (8-49)	7 (4-15)	8 (7-13)
Overall survival, median (95% CI), mo	37 (23-59)	17 (10-33)	69 (36-95)	39 (16-NE)	37 (26-52)

Abbreviations: BUFLU = busulfan-fludarabine; CY = cyclophosphamide; FLUMEL = fludarabine-melphalan; VP16 = etoposide.
* Missing: BUFLU (n = 3), FLUMEL (n = 1), CY (n = 2), VP16 (n = 2), and total (n = 8).

Table 3 Follow-up time and survival by diagnosis*

Outcome	ALL (n = 127)	AML (n = 201)	MDS (n = 105)	NHL (n = 118)	Total (N = 622)
Follow-up time, median (95% CI), mo	69 (54-85)	44 (36-59)	37 (30-50)	99 (67-148)	60 (51-63)
Progression-free survival, median (95% CI), mo†	13 (7-17)	7 (5-9)	8 (6-22)	8 (6-18)	8 (7-13)
Overall survival, median (95% CI), mo	80 (31-NE)	24 (16-51)	31 (19-64)	37 (16-70)	37 (26-52)

Abbreviations: ALL = acute lymphocytic leukemia; AML = acute myelocytic leukemia; MDS = myelodysplastic syndrome; NE = not estimible; NHL = non-Hodgkin lymphoma.
* Other diagnoses are omitted (n = 70).
† Missing: ALL (n = 3), AML (n = 2), MDS (n = 0), NHL (n = 2), Other (n = 1), and total (n = 8).

Table 4 CTCAE severity of adverse effects by regimen

Adverse effect	BUFLU, No. (%)(n = 330)	CY, No. (%)(n = 112)	FLUMEL, No. (%)(n = 85)	VP16, No. (%)(n = 95)	Total, No. (%)(N = 622)	*P* value
Dermatitis radiation						
Grade 0	330 (100.0)	111 (99.1)	85 (100.0)	95 (100.0)	621 (99.8)	.21*
Grade 2	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.2)	
Alopecia						
Grade 0	246 (74.5)	88 (78.6)	68 (80.0)	74 (77.9)	476 (76.5)	.35†
Grade 1	5 (1.5)	1 (0.9)	0 (0.0)	0 (0.0)	6 (1.0)	
Grade 2	79 (23.9)	23 (20.5)	17 (20.0)	21 (22.1)	140 (22.5)	
Febrile neutropenia						
Grade 0	199 (60.3)	85 (75.9)	49 (57.6)	55 (57.9)	388 (62.4)	.49†
Grade 1	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	
Grade 2	2 (0.6)	1 (0.9)	0 (0.0)	1 (1.1)	4 (0.6)	
Grade 3	127 (38.5)	26 (23.2)	35 (41.2)	38 (40.0)	226 (36.3)	
Grade 4	1 (0.3)	0 (0.0)	1 (1.2)	1 (1.1)	3 (0.5)	
Lung infection						
Grade 0	211 (63.9)	82 (73.2)	52 (61.2)	59 (62.1)	404 (65.0)	.29†
Grade 1	7 (2.1)	1 (0.9)	1 (1.2)	0 (0.0)	9 (1.4)	
Grade 2	86 (26.1)	24 (21.4)	20 (23.5)	19 (20.0)	149 (24.0)	
Grade 3	20 (6.1)	4 (3.6)	8 (9.4)	14 (14.7)	46 (7.4)	
Grade 4	4 (1.2)	1 (0.9)	4 (4.7)	2 (2.1)	11 (1.8)	
Grade 5	2 (0.6)	0 (0.0)	0 (0.0)	1 (1.1)	3 (0.5)	
Pneumonitis						
Grade 0	300 (90.9)	102 (91.1)	77 (90.6)	81 (85.3)	560 (90.0)	0.14†
Grade 1	18 (5.5)	5 (4.5)	2 (2.4)	5 (5.3)	30 (4.8)	
Grade 2	9 (2.7)	3 (2.7)	4 (4.7)	5 (5.3)	21 (3.4)	
Grade 3	2 (0.6)	1 (0.9)	1 (1.2)	3 (3.2)	7 (1.1)	
Grade 4	0 (0.0)	1 (0.9)	1 (1.2)	0 (0.0)	2 (0.3)	
Grade 5	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.1)	2 (0.3)	
Oral mucositis						
Grade 0	76 (23.0)	44 (39.3)	31 (36.5)	16 (16.8)	167 (26.8)	<.001†
Grade 1	81 (24.5)	9 (8.0)	8 (9.4)	1 (1.1)	99 (15.9)	
Grade 2	128 (38.8)	43 (38.4)	35 (41.2)	36 (37.9)	242 (38.9)	
Grade 3	44 (13.3)	14 (12.5)	10 (11.8)	38 (40.0)	106 (17.0)	
Grade 4	1 (0.3)	2 (1.8)	1 (1.2)	4 (4.2)	8 (1.3)	
Nausea						
Grade 0	33 (10.0)	51 (45.5)	7 (8.2)	26 (27.4)	117 (18.8)	.67†
Grade 1	140 (42.4)	7 (6.3)	19 (22.4)	19 (20.0)	185 (29.7)	
Grade 2	150 (45.5)	54 (48.2)	57 (67.1)	48 (50.5)	309 (49.7)	
Grade 3	7 (2.1)	0 (0.0)	2 (2.4)	2 (2.1)	11 (1.8)	

(*continued on next page*)

Table 4 (*Continued*)

Adverse effect	BUFLU, No. (%)(n = 330)	CY, No. (%)(n = 112)	FLUMEL, No. (%)(n = 85)	VP16, No. (%)(n = 95)	Total, No. (%)(N = 622)	*P* value
Diarrhea						
Grade 0	117 (35.5)	69 (61.6)	25 (29.4)	63 (66.3)	274 (44.1)	.05†
Grade 1	127 (38.5)	3 (2.7)	21 (24.7)	10 (10.5)	161 (25.9)	
Grade 2	84 (25.5)	37 (33.0)	35 (41.2)	18 (18.9)	174 (28.0)	
Grade 3	2 (0.6)	3 (2.7)	4 (4.7)	4 (4.2)	13 (2.1)	
ARDS						
Grade 0	301 (91.2)	105 (93.8)	79 (92.9)	86 (90.5)	571 (91.8)	.98†
Grade 3	16 (4.8)	6 (5.4)	2 (2.4)	4 (4.2)	28 (4.5)	
Grade 4	12 (3.6)	1 (0.9)	4 (4.7)	4 (4.2)	21 (3.4)	
Grade 5	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.1)	2 (0.3)	
Cystitis, noninfective						
Grade 0	322 (97.6)	108 (96.4)	84 (98.8)	89 (93.7)	603 (96.9)	.16†
Grade 1	3 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	4 (0.6)	
Grade 2	1 (0.3)	2 (1.8)	0 (0.0)	3 (3.2)	6 (1.0)	
Grade 3	4 (1.2)	1 (0.9)	1 (1.2)	3 (3.2)	9 (1.4)	
Cataracts						
No	269 (81.5)	94 (83.9)	75 (88.2)	83 (87.4)	521 (83.8)	.34*
Yes	61 (18.5)	18 (16.1)	10 (11.8)	12 (12.6)	101 (16.2)	
Secondary malignancy						
No	328 (99.4)	112 (100.0)	85 (100.0)	95 (100.0)	620 (99.7)	.62*
Yes	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	
Pulmonary fibrosis						
Grade 0	310 (93.9)	108 (96.4)	84 (98.8)	92 (96.8)	594 (95.5)	.07†
Grade 1	13 (3.9)	0 (0.0)	0 (0.0)	2 (2.1)	15 (2.4)	
Grade 2	2 (0.6)	3 (2.7)	0 (0.0)	1 (1.1)	6 (1.0)	
Grade 3	2 (0.6)	1 (0.9)	0 (0.0)	0 (0.0)	3 (0.5)	
Grade 4	2 (0.6)	0 (0.0)	1 (1.2)	0 (0.0)	3 (0.5)	
Grade 5	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	

Abbreviations: ARDS = acute respiratory distress syndrome; BUFLU = busulfan-fludarabine; CTCAE = Common Terminology Criteria for Adverse Events; CY = cyclophosphamide; FLUMEL = fludarabine-melphalan; VP16 = etoposide.

* Chi-square test for differences in proportions.

† Cuzick test for differences in trend in proportions.

Table 5 CTCAE severity of effects grouped by clinical significance

Adverse effect	BUFLU, No. (%)(n = 330)	CY, No. (%)(n = 112)	FLUMEL, No. (%)(n = 85)	VP16, No. (%)(n = 95)	Total, No. (%)(N = 622)	*P* value*
Dermatitis radiation						
Grade 0-2	330 (100.0)	112 (100.0)	85 (100.0)	95 (100.0)	622 (100.0)	-
Alopecia						
Grade 0-2	330 (100.0)	112 (100.0)	85 (100.0)	95 (100.0)	622 (100.0)	-
Febrile neutropenia						
Grade 0-2	202 (61.2)	86 (76.8)	49 (57.6)	56 (58.9)	393 (63.2)	.010
Grade 3-5	128 (38.8)	26 (23.2)	36 (42.4)	39 (41.1)	229 (36.8)	
Lung infection						
Grade 0-2	304 (92.1)	107 (95.5)	73 (85.9)	78 (82.1)	562 (90.4)	.003
Grade 3-5	26 (7.9)	5 (4.5)	12 (14.1)	17 (17.9)	60 (9.6)	
Pneumonitis						
Grade 0-2	327 (99.1)	110 (98.2)	83 (97.6)	91 (95.8)	611 (98.2)	.18
Grade 3-5	3 (0.9)	2 (1.8)	2 (2.4)	4 (4.2)	11 (1.8)	
Oral mucositis						
Grade 0-2	285 (86.4)	96 (85.7)	74 (87.1)	53 (55.8)	508 (81.7)	<.001
Grade 3-5	45 (13.6)	16 (14.3)	11 (12.9)	42 (44.2)	114 (18.3)	
Nausea						
Grade 0-2	323 (97.9)	112 (100.0)	83 (97.6)	93 (97.9)	611 (98.2)	.48
Grade 3-5	7 (2.1)	0 (0.0)	2 (2.4)	2 (2.1)	11 (1.8)	
Diarrhea						
Grade 0-2	328 (99.4)	109 (97.3)	81 (95.3)	91 (95.8)	609 (97.9)	.034
Grade 3-5	2 (0.6)	3 (2.7)	4 (4.7)	4 (4.2)	13 (2.1)	
ARDS						
Grade 0-2	301 (91.2)	105 (93.8)	79 (92.9)	86 (90.5)	571 (91.8)	.78
Grade 3-5	29 (8.8)	7 (6.3)	6 (7.1)	9 (9.5)	51 (8.2)	
Cataracts						
No	269 (81.5)	94 (83.9)	75 (88.2)	83 (87.4)	521 (83.8)	.34
Yes	61 (18.5)	18 (16.1)	10 (11.8)	12 (12.6)	101 (16.2)	
Cystitis, noninfective						
Grade 0-2	326 (98.8)	111 (99.1)	84 (98.8)	92 (96.8)	613 (98.6)	.50
Grade 3-5	4 (1.2)	1 (0.9)	1 (1.2)	3 (3.2)	9 (1.4)	
Secondary malignancy						
No	328 (99.4)	112 (100.0)	85 (100.0)	95 (100.0)	620 (99.7)	.62
Yes	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	
Pulmonary fibrosis						
Grade 0-2	325 (98.5)	111 (99.1)	84 (98.8)	95 (100.0)	615 (98.9)	.66
Grade 3-5	5 (1.5)	1 (0.9)	1 (1.2)	0 (0.0)	7 (1.1)	

Abbreviations: ARDS = acute respiratory distress syndrome; BUFLU = busulfan-fludarab; CTCAE = Common Terminology Criteria for Adverse Events; CY = cyclophosphamide; FLUMEL = fludarabine-melphalan; VP16 = etoposide.

* χ^2 test for difference in proportions.

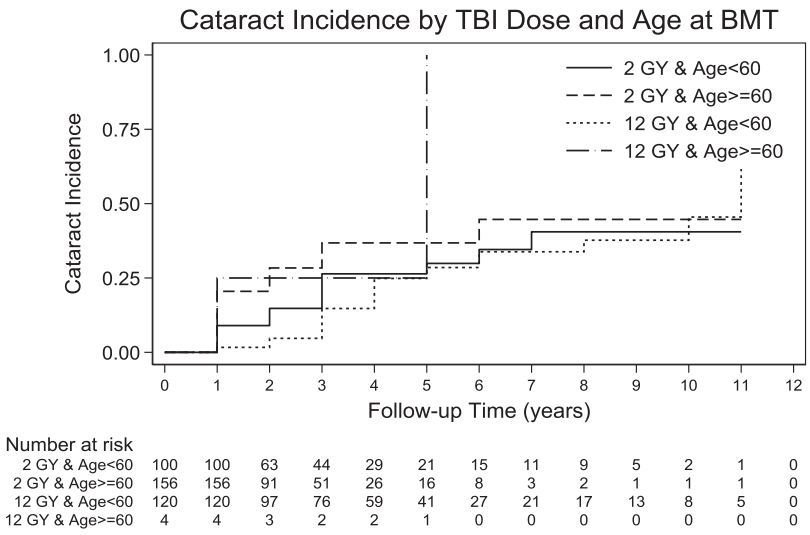

Figure 1 Cataract incidence by total body irradiation dose and age at BMT. *Abbreviation*: BMT = bone marrow transplant.

Gy 26%, CY 33%, VP16 19%). Grade 3 to 5 oral mucositis was most common among patients in the VP16 12 Gy group (44%) compared to each of the other groups (each < 15%) ($P < .001$). ARDS occurred infrequently, with more than 90% of patients not experiencing it. However, there were 2 cases of grade 5 ARDS in the cohort. There were no identifiable risk factors in the 2 patients who had grade 5 ARDS. Noninfective cystitis occurred at a very low rate, with the vast majority of patients not experiencing it.

Subacute and late adverse effects

Pneumonitis occurred infrequently among the different treatment groups, with less than 10% of patients in the BUFLU 2 Gy, FLUMEL 2 Gy, and CY 12 Gy groups experiencing it. Lung blocking was used in patients receiving the high-dose regimens, resulting in an estimated mean lung dose of 8 to 9 Gy (50 patients [26%] in the high-dose cohorts did not receive lung blocking). Approximately 15% of patients in the VP16 12 Gy group experienced any grade of pneumonitis. Pneumonitis was primarily low grade, with few cases greater than grade 3. Two cases of grade 5 pneumonitis were observed. There was no statistically significant difference between regimens in pneumonitis rate or severity. Cataract formation occurred in 16% of patients and the difference between regimens was small and not statistically significant. However, the median time to cataract onset was significantly lower for the BUFLU 2 Gy and FLUMEL 2 Gy regimens (1 to 1.5 years) compared with the CY group (3 to 4 years). Regimens administered at a radiation dose of 12 Gy were associated with greater cataract formation than regimens administered at lower radiation dose ($P = .02$). However, age was found to modify the association, and when age was added as a second predictor, the difference was reduced and no longer statistically significant ($P = .80$; Fig 1). The secondary malignancy rate was low; only 2 cases of confirmed secondary malignancy occurred in the entire cohort, both in the BUFLU 2 Gy regimen. One cancer was a T1 oral tongue squamous cell carcinoma and the other was cancer of the buccal mucosa. The patient who developed oral tongue cancer had previously undergone transplantation 6 years earlier. Treatment consisted of hemiglossectomy and selective neck dissection. The patient was alive at the last follow-up in early 2021. One thyroid nodule was noted in the CY 12 Gy group, but pathologic or radiologic diagnosis was not available. Pulmonary fibrosis occurred relatively infrequently in the cohort at a rate of less than 5% overall, and there was no statistically significant difference between the different regimens.

Discussion

Total body irradiation has been a mainstay of stem cell transplantation for several decades. During this period, several potential acute and late toxicities of radiation have been identified. Early adverse effects include dermatitis, alopecia, nausea, diarrhea, and oral mucositis.[4,5] Subacute and late toxicities of varying incidence and severity have also been reported in association with TBI, and these include cardiovascular disease, pneumonitis, secondary malignancy, cataract formation, decreased fertility, osteoporosis, and endocrine disorders.[4-8] Of these toxicities, pneumonitis, secondary malignancy, and cataract formation have been the focus of several reports.

Early adverse effects

In general, radiation dermatitis was not experienced in this cohort of patients. This outcome is likely related to

the low dose of radiation (2 Gy) received by a majority of the cohort and the fractionated nature of the dose of the 12-Gy regimens. Deeg reported in 1983 that many patients experience a mild skin erythema a few days after irradiation.[4] However, this observation is likely dated because radiation delivery, dose, fractionation, and chemotherapy have changed substantially since the 1980s.

A large proportion of patients in this study experienced nausea and diarrhea. Approximately 20% of patients experienced grade 2 alopecia. Nausea, diarrhea, and alopecia have been reported as acute effects of both TBI and associated chemotherapy.[4] However, determining the causative agent (chemotherapy vs radiation) is difficult owing to the close temporal proximity of administration of both aspects of the preparative regimen.

Oral mucositis was the only early adverse effect in which a large difference in incidence and severity was found between the 4 different preparative regimens. Approximately 44% of patients who received the VP16 12 Gy regimen experienced grade 3 or 4 oral mucositis, whereas fewer than 15% of patients on each of the other regimens did. Mucositis has been recognized as one of the most common adverse effects related to the administration of myeloablative chemotherapy and radiation.[1,3,10,11] In 1993, Woo et al reported an approximate 75% incidence of oral mucositis in patients with stem cell transplants who received myeloablative preconditioning.[12] Woo et al also remarked that incidences ranging from 28.6% to 100% have been reported. The higher rate of oral mucositis in the current study's cohort is likely related to the administration of etoposide. Hoyt et al reported a higher risk of oral mucositis when comparing an etoposide-based regimen to a cyclophosphamide-based myeloablative regimen.[10]

Late adverse effects

Pneumonitis rates were relatively low in this study's cohort and did not differ based on the preparative regimen received. A total of 11 cases (1.8%) had pneumonitis of grade 3 or greater. Even among the 12-Gy fractionated regimens, pneumonitis rates were low, which can likely be attributed to the use of lung shielding. Several studies in the literature have addressed the issue of pulmonary toxicity in TBI.[7,8,13-22] Rates of pneumonitis vary considerably throughout the literature. The considerable variation is likely due to the multifactorial nature of pulmonary toxicity related to stem cell transplantation as there are several variables related to patient characteristics, chemotherapy regimen, and radiation delivery.[14-23] Regarding radiation therapy, there is some debate about the potential factors that may contribute to interstitial pneumonitis, including dose rate, mean lung dose, and fractionation.[15,16,18-23] Three factors likely contributed to the relatively low rates of pneumonitis in the current study's cohort. First, the majority of patients were treated with 2 Gy of TBI. Second, this study's dose rates would likely be considered low according to the literature, although the contribution of dose rate to pneumonitis risk is an area that has shown heterogeneous results. The definition of low dose rate also has not been definitively established; dose rates that are considered low range from <4.8 cGy/min to 15 cGy/min.[18,19,23-26] Our dose rate ranged from 2 cGy/min to 15 cGy/min from 1995 to 2017. Third, patients receiving the higher dose 12 Gy regimens were delivered using multiple fractions, and pulmonary shielding was used for the majority of patients to reduce the mean lung dose to 8 to 9 Gy. Studies regarding the use of lung blocking have also been contradictory, but the mean lung dose has been shown to be correlated with pulmonary toxicity.[19,20,22] Further analysis regarding potential causative factors of pneumonitis in this study's cohort was not possible owing to the low rate of clinically significant pneumonitis.

Cataract rates within the cohort were relatively high; 101 patients (16%) developed cataracts, with a median time to cataract formation of 1 to 4 years. The median time to cataract formation was earlier in the 2-Gy regimens. However, these regimens consisted of older patients, which likely contributed to their earlier onset of cataracts. When age at bone marrow transplant was added to the model for time to cataracts, an age of 60 years or older became an important predictor (hazard ratio [HR], 1.81; 95% CI, 1.1-3.0; $P = .02$), and the 12-Gy dosage was no longer statistically significant (HR, 0.85; 95% CI, 0.59-1.45; $P = .55$).

Review of the literature shows significant heterogeneity regarding cataract formation. Risk of cataractogenesis after TBI has been reported in the range of 2% to 94%, with variations in dose, fractionation, dose rate, preparative regimen, and diagnosis.[5-8,27-30] The median time to onset of cataract formation has ranged from 2.2 to 5 years.[6,7,27,28,31] The role of fractionation and dose has been discussed in several articles. Although these studies differ, fractionation seems to be associated with a lower rate of cataract occurrence.[7,8,27,28] Dose rate has also been examined, and there is some evidence that an increased dose rate may be associated with an increased risk of cataractogenesis.[29,31] Steroid use has also been implicated in the occurrence of cataracts after stem cell transplant.[27]

Regarding secondary malignancy, we had a relatively low rate, with only 2 patients experiencing a secondary malignancy. There is significant heterogeneity in the published literature regarding the risk of secondary malignancy after TBI; some series have reported increased risk, and others have not reported any cases of secondary malignancies.[5,7,30,32,33] A recent, large retrospective study from the University of Washington reported a cumulative incidence of secondary malignancies of 22.0% by 30 years after stem cell transplantation. Further analysis showed

that radiation dose and fractionation were related to the incidence of secondary malignancies. Lower doses and fractionated schedules were shown to have lower risks of secondary cancers. TBI doses in the range of 200 to 450 cGy did not differ significantly from regimens of chemotherapy alone in terms of secondary-malignancy risk.[32]

The low rate of secondary malignancy found in this study is similar to that of other studies with median follow-up times of 6 or fewer years.[5,30] However, this study's results differ from the analysis of Bölling et al, who reported a 10% rate of secondary malignancy with a mean time to event of 38 months. The authors noted that their reported rate of secondary malignancy was higher than most reports in the literature.[7] The low rate of secondary malignancy in the current study is likely attributable to several factors. First, a majority of the patient cohort received only 2 Gy of TBI. This dose was found to be correlated with the lowest incidence of secondary malignancy in a recent study from the University of Washington.[32] That study found that the rate of secondary malignancy was not statistically different in patients receiving 200 to 450 cGy TBI compared with those receiving chemotherapy-only regimens. Second, patients in the current study who received the 12-Gy regimen were treated in a fractionated manner, which has been shown to be related to a lower risk of secondary cancer compared with single-fraction regimens of a similar dose. Patients treated with 600 to 1200 cGy fractionated TBI were found to have an HR of secondary malignancy of 1.67 compared with patients receiving only chemotherapy.[32] Third, as shown by other studies with a relatively short follow-up time, a 5-year median follow-up is likely too short to capture a significant number of events that may take decades to occur.[34] Finally, as a retrospective study, this study's data are at risk of ascertainment bias, in which not all cases of secondary malignancies may have been reported for various reasons pertaining to how each individual patient was followed after receiving TBI.

Limitations of this study are primarily related to the retrospective nature of the data. There was substantial heterogeneity in the patient population regarding age, diagnosis, preparative regimen, radiation dose, radiation fractionation, and use of lung blocking. In addition, during the two decades during which the data were collected, medical management likely changed, which may introduce a potential bias. Differences regarding survival and adverse effects between regimens should be considered more descriptive than comparative, owing to likely indication bias. Because this was a retrospective study, there also may have been differences in charting and reporting of various toxicities.

Strengths of this study include its large size, comprehensive and standardized grading of toxicity, and use of modern treatment techniques and regimens. To our knowledge, this study represents one of the largest reported cohorts of patients receiving TBI.

Conclusions

In this large and comprehensive evaluation of toxicities related to TBI in a single patient cohort, the data showed relatively low rates of radiation-related toxicities such as interstitial pneumonitis and secondary malignancy. However, there were significant rates of cataractogenesis and a relatively short onset time to the development of cataracts. On univariable analysis, cataract formation appeared to be dose-dependent. However, when age was added as a second predictor, dose was no longer a statistically significant predictor. These results can be used to inform patients of the potential adverse effects, both early and late, related to TBI and stem cell transplant.

References

1. 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.
2. Wills C, Cherian S, Yousef J, Wang K, Mackley HB. Total body irradiation: A practical review. *Appl Radiat Oncol*. 2016:11–17.
3. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354:1813–1826.
4. Deeg HJ. Acute and delayed toxicities of total body irradiation. *Int J Radiat Oncol*. 1983;9:1933–1939.
5. De Felice 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.
6. Leiper AD. Late effects of total body irradiation. *Arch Dis Child*. 1995;72:382–385.
7. Bölling T, Kreuziger DC, Ernst I, Elsayed H, Willich N. Retrospective, monocentric analysis of late effects after total body irradiation (TBI) in adults. *Strahlentherapie und Onkol*. 2011;187:311–315.
8. Thomas O, Mahé M-A, Campion L, et al. Long-term complications of total body irradiation in adults. *Int J Radiat Oncol*. 2001;49:125–131.
9. National Cancer Institute, National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE). *NIH Publ*. 2010:0–71. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Accessed 3 March 2018.
10. Hoyt R, Ritchie DS, Wirth A, Szer J, Grigg AP. Etoposide induces more severe mucositis than CY when added to TBI as conditioning in allograft recipients receiving CsA and MTX. *Bone Marrow Transplant*. 2010;45:1457–1462.
11. Cutler C, Li S, Kim HT, et al. Mucositis after allogeneic hematopoietic stem cell transplantation: A cohort study of methotrexate- and non-methotrexate-containing graft-versus-host disease prophylaxis regimens. *Biol Blood Marrow Transplant*. 2005;11:383–388.
12. Woo S-B, Sonis ST, Monopoli MM, Sonis AL. A longitudinal study of oral ulcerative mucositis in bone marrow transplant recipients. *Cancer*. 1993;72:1612–1617.
13. Ujaimi RK, Isfahanian N, Russa DJL, Samant R, Bredeson C, Genest P. Pulmonary toxicity following total body irradiation for acute lymphoblastic leukaemia: The Ottawa Hospital Cancer Centre (TOHCC) experience. *J Radiother Pract*. 2016;15:54–60.
14. 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;6:1–11.
15. Morgan TL, Falk PM, Kogut N, Shah KH, Tome M, Kagan AR. A comparison of single-dose and fractionated total-body irradiation on the development of pneumonitis following bone marrow transplantation. *Int J Radiat Oncol Biol Phys*. 1996;36:61–66.
16. Gopal R, Ha CS, Tucker SL, et al. Comparison of two total body irradiation fractionation regimens with respect to acute and late pulmonary toxicity. *Cancer*. 2001;92:1949–1958.
17. Byun HK, Yoon HI, Cho J, et al. Factors associated with pulmonary toxicity after myeloablative conditioning using fractionated total body irradiation. *Radiat Oncol J*. 2017;35:257–267.
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. Oya N, Sasai K, Tachiiri S, et al. Influence of radiation dose rate and lung dose on interstitial pneumonitis after fractionated total body irradiation: Acute parotitis may predict interstitial pneumonitis. *Int J Hematol*. 2006;83:86–91.
20. Weshler Z, Breuer R, Or R, et al. Interstitial pneumonitis after total body irradiation: Effect of partial lung shielding. *Br J Haematol*. 1990;74:61–64.
21. Ozsahin M, Belkacémi Y, Pène F, et al. Interstitial pneumonitis following autologous bone-marrow transplantation conditioned with cyclophosphamide and total-body irradiation. *Int J Radiat Oncol*. 1996;34:71–77.
22. Della Volpe A, Ferreri AJM, 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.
23. Cosset J-M, Socie G, Dubray B, Girinsky T, Fourquet A, Gluckman E. Single dose versus fractionated total body irradiation before bone marrow transplantation: Radiobiological and clinical considerations. *Int J Radiat Oncol*. 1994;30:477–492.
24. Carruthers SA, Wallington MM. Total body irradiation and pneumonitis risk: A review of outcomes. *Br J Cancer*. 2004;90:2080–2084.
25. 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;13:1–9.
26. Gogna NK, Morgan G, Downs K, Atkinson K, Biggs J. Lung dose rate and interstitial pneumonitis in total body irradiation for bone marrow transplantation. *Australas Radiol*. 1992;36:317–320.
27. Benyunes MC, Sullivan KM, Joachim Deeg H, et al. Cataracts after bone marrow transplantation: Long-term follow-up of adults treated with fractionated total body irradiation. *Int J Radiat Oncol*. 1995;32:661–670.
28. Zierhut D, Lohr F, Schraube P, et al. Cataract incidence after total-body irradiation. *Int J Radiat Oncol Biol Phys*. 2000;46:131–135.
29. Ozsahin M, Belkacemi Y, Pens F, et al. Total-body irradiation and cataract incidence: A randomized comparison of two instantaneous dose rates. *Int J Radiat Oncol Biol Phys*. 1994;28:343–347.
30. Marnitz S, Zich A, Martus P, et al. Long-term results of total body irradiation in adults with acute lymphoblastic leukemia. *Strahlentherapie und Onkol*. 2014;190:453–458.
31. Belkacémi Y, Ozsahin M, Pène F, et al. Cataractogenesis after total body irradiation. *Int J Radiat Oncol Biol Phys*. 1996;35:53–60.
32. Baker KS, Leisenring WM, Goodman PJ, et al. Total body irradiation dose and risk of subsequent neoplasms following allogeneic hematopoietic cell transplantation. *Blood*. 2019;133(26):2790–2799.
33. Pommier P, Sunyach MP, Pasteuris C, Frappaz D, Carrie C. Second cancer after total-body irradiation (TBI) in childhood. *Strahlentherapie und Onkol*. 2009;185(Suppl 2):13–16.
34. Dracham CB, Shankar A, Madan R. Radiation induced secondary malignancies: A review article. *Radiat Oncol J*. 2018;36:85–94.