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Does Total Body Irradiation Conditioning Improve Outcomes of Myeloablative HLA-Identical Sibling Transplants for Chronic Lymphocytic Leukemia?

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Abstract

An allogeneic hematopoietic cell transplant (HCT) from an HLA-identical donor after high-dose (myeloablative) pre-transplant conditioning, is an effective therapy for some people with chronic lymphocytic leukemia (CLL). Because CLL is a highly radiosensitive cancer, we hypothesized total body irradiation (TBI) conditioning regimens may be associated with better outcomes than those without TBI. To answer this we analyzed data from 180 subjects with CLL receiving myeloablative doses of TBI (N=126) or not (N=54), transplanted from an HLA-identical sibling donor, between 1995 and 2007 and reported to the Center for International Blood & Marrow Transplant Research (CIBMTR). At 5 years, treatment-related mortality was 48% (95% CI, 39–57%) *vs.* 50% (95% CI, 36–64%); p=NS. Relapse rates were 17% (95% CI, 11–25%) *vs.* 22% (95% CI, 11–35%); p=NS. Five-year progression-free survival and overall survival was 34% (95% CI, 26–43%) *vs.* 28% (95% CI, 15–42%); p=NS and 42% (95% CI, 33–51%) *vs.* 33% (95% CI, 19–48%); p=NS, respectively. The single most common cause of death in both cohorts was recurrent/progressive CLL. No variable tested in the multivariate analysis was found to significantly affect these outcomes including having failed fludarabine. Within the limitations of this study we found no difference in HLA-identical sibling transplant outcomes between myeloablative TBI and chemotherapy pre-transplant conditioning in persons with CLL.

Introduction

Hematopoietic cell transplants from a human leukocyte antigen (HLA)-identical sibling are effective therapy for selected persons with chronic lymphocytic leukemia (CLL)[1–8]. Myeloablative conditioning regimens, with or without total body irradiation (TBI), were commonly used, in the past. Although reduced-intensity regimens are increasingly-used, data from transplants using myeloablative conditioning are mature for analysis. Most TBI regimens also contain cyclophosphamide [9–11]. Myeloablative regimens without TBI (referred to herein as chemotherapy (CT)) typically include busulfan, often, but not always with cyclophosphamide [12,13]. Two small retrospective studies comparing these conditioning regimens showed no difference or favored a TBI-based conditioning regimen [12,14].

TBI may be especially effective in highly radio-sensitive cancers such as CLL [15–17]. Consequently, we hypothesized that TBI-containing conditioning regimens may have better outcomes than CT conditioning regimens. We compared transplant outcomes of these two conditioning regimens in subjects reported to the CIBMTR.

Methods

Data Sources

The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program (NMDP). CIBMTR comprises a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplants to a centralized Statistical Center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule. Additional details regarding the data source are described elsewhere [18].

Inclusion Criteria

180 patients with CLL (Richter's transformation and pro-lymphocytic leukemia were excluded) who received a conventional myeloablative (no reduced-intensity) allogeneic transplant from an HLA-identical sibling between 1995 and 2007 were included. This population was extracted from an initially larger cohort of 1,260 subjects reported to the CIBMTR. Unrelated donor transplants were excluded because of too many missing pieces of data, leaving us with 619 subjects. Further exclusions included twin and other related donors (N=42), cord blood donors (N=31), subjects with missing survival data (N=1), subjects with missing data on regimen intensity (N=25), lack of informed consent (N=68), subjects with ex *vivo* T-cell depleted grafts (N=62) and less intensive conditioning (N=210). Completeness index was 77% overall with good follow-up in both cohorts of 91% at 3 years and 84% at 5 years post-transplant[19].

Definitions of variables and outcomes

Rai stage and Karnofsky Performance score were categorized as previously described [20,21]. Constitutional symptoms included unexplained weight loss of >10% of body weight within 6 months, fever (>38°C) or night sweats. Refractoriness to fludarabine was defined as having stable or progressive disease after fludarabine-based therapy at any stage of treatment, as reported by the participating centers. Refractoriness to the prior therapy was defined as stable or progressive disease after the most recent therapy as reported by the participating centers. Myeloablative pre-transplant conditioning regimens are defined according to the CIBMTR Reduced-Intensity Conditioning Regimen Workshop[22,23].

Endpoints were measured from the time of transplant. For survival, subjects were considered to have an event at time of death from any cause. Survivors were censored at last contact. Relapse was defined by standard criteria and treatment-related mortality (TRM) was considered a competing event. TRM was defined as death without leukemia recurrence. Relapse was considered a competing event. PFS was defined as time to treatment-failure (death or relapse). Overall survival (OS) was defined as time to death from any cause. For relapse, TRM, and PFS, subjects alive in continuous complete remission were censored at last follow-up. Neutrophil recovery was defined as the first day of neutrophils $\geq 0.5 \times 10^9$/L for 3 consecutive days. Platelet recovery was defined as achieving platelets$>20 \times 10^9$/L

without platelet transfusions for 7 days. Acute and chronic graft *vs.* host disease (G*v*HD) were graded as described[24,25]. For engraftment and G*v*HD, death without the event was considered a competing event.

Data Analysis

Subject-, disease- and transplant-related variables of the TBI and CT cohorts were compared using the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. TRM, relapse, engraftment, acute and chronic G*v*HD were estimated as cumulative incidences taking into account competing risks. Probabilities of PFS and survival were calculated using the Kaplan-Meier estimator with variance estimated by the Greenwood formula. Survival curve estimates were compared using the log-rank test. Multivariate analyses were conducted to identify significant predictors of hematopoietic recovery, acute and chronic G*v*HD, TRM, relapse, PFS, and OS.

The proportional hazards model was built by forcing the main effect variable (TBI *vs.* CT) into the model. Backward elimination with a criterion of $p<0.05$ for retention was used to select a final model. The following variables were analyzed for their prognostic value on each of the outcomes: subject-related variables (age, gender and Karnofsky performance score at transplant), disease-related variables (Rai stage at diagnosis, Rai stage at transplant, constitutional symptoms at diagnosis, elevated LDH at transplant, splenectomy, refractoriness to fludarabine, and disease state at transplant) and transplant-related variables (time from diagnosis to transplant, donor age, donor-recipient gender and CMV serology, year of transplant and G*v*HD prophylaxis). None of the variables with >20% missing information were included in the model.

Results and Discussion

Demographic features of the cohorts are shown in Table 1. Median ages were 48 and 49 years with a male predominance, in both groups. Most subjects had early Rai stage at diagnosis (66% *vs.* 54%) without B-symptoms (60% *vs.* 63%). Both cohorts had a median of 3 prior therapies and most were resistant to their last therapy (75% *vs.* 77%), did not have a splenectomy (91% for both) and a similar proportion had failed fludarabine (45% *vs.* 50%, respectively). The proportions of subjects in complete or partial remission pre-transplant were similar, 46% and 44%.

Most subjects in the TBI cohort received cyclophosphamide. Ninety-six percent of subjects in the CT cohort received a busulfan-based regimen which was given orally in 48%, intravenously in 28% and not reported in 24%. Fifty percent of TBI subjects received blood cell grafts *vs.* 72% of CT subjects ($p=0.006$). Fifteen percent of subjects in the CT cohort received anti-thymocyte globulin (ATG) pre-transplant *vs.* none in the TBI cohort ($p<0.001$).

One hundred day cumulative incidences of neutrophil recovery in the TBI and CT cohorts were similar, (98% (95% CI, 95–100%) and 96% (95% CI, 90–100%); $p=0.45$). Corresponding 100-day cumulative incidences of platelet recovery were 82% (95% CI, 74–88%) and 83% (95% CI, 72–91%); $p=0.86$. Five-year TRM rates were 48% (95% CI, 39–

57%) *vs.* 50% (95% CI, 36–64%); p=NS. One hundred day rates of ≥grade-2 acute G*v*HD were similar, 49% (95% CI, 41–58%) v*s.* 43% (95% CI, 30–57%); p=0.47. One-year incidence of chronic GVHD was 45% (95%, CI 36–54%) *vs.* 37% (95% CI, 24–51%); p=0.14. Five-year relapse rates were 17% (95% CI, 11–25%) *vs.* 22% (95% CI, 11–35%); p=NS. Five-year PFS was 34% (95% CI, 26–43%) *vs.* 28% (95% CI, 15–42%); p=NS. Five-year OS was 42% (95% CI, 33–51%) *vs.* 33% (95% CI, 19–48%); p=NS (see Figure).

The proportion of deaths in both cohorts was similar at 61% and 65% (see Table 2). The single most frequent cause of death was relapse. However, the pattern of other causes of deaths differed between the two groups: the TBI cohort had more deaths from infection, adult respiratory distress syndrome (ARDS) and G*v*HD whereas the CT cohort had more deaths from organ failure, hemorrhage and liver veno-occlusive disease. No factor tested significantly affected reported outcomes including having failed fludarabine (Table 3). New cancers occurred in both cohorts (TBI=11 vs. CT=3). Rates were not significantly different but this conclusion is limited by the small cohorts. A total of 4 deaths from new cancers occurred only in the TBI cohort (acute lymphoblastic leukemia [N=1], breast cancer [N=1], gastrointestinal cancer [N=1] and other cancer [N=1].

In summary, we found no significant differences in outcomes after myeloablative HLA-identical sibling transplants for CLL using TBI-containing or CT conditioning regimens. The strength of our conclusion is tempered by the small sample size, especially in the CT cohort with resultant low power to detect possible differences. A larger observational data set to address this question is unlikely to evolve because of a shift to less intensive conditioning and because no randomized study is likely to be done.

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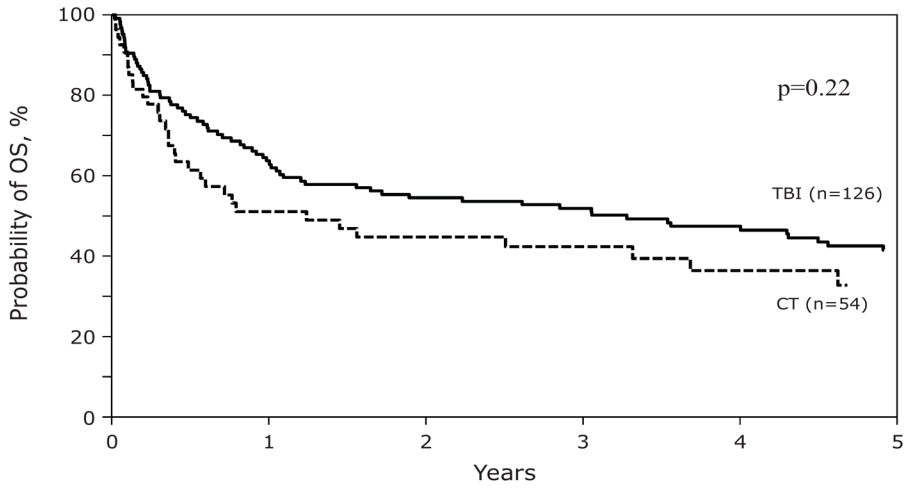

Figure.
Adjusted Survival

Table 1

Subject-, Disease- and Transplant-Related Variables

Variable	TBI	CT	p-value
Subject-related			
N subjects	126	54	
N centers	65	24	
Age, median(range), years	48 (24–64)	49 (27–62)	0.38
Gender			
Male	86	41	0.30
Karnofsky score pre-transplant			0.41
<90%	41	19	
>=90%	81	35	
Missing	4	0	
Disease-related			
Rai stage at diagnosis			0.19
Early Rai stages	83	29	
Late Rai stages	24	11	
Missing	19	14	
Rai stage pre-transplant			0.46
Early	73	29	
Advanced	41	22	
Missing	12	3	
Constitutional-symptoms at diagnosis			0.63
Absent	76	34	
Present	26	8	
Unknown	24	12	
Elevated LDH at transplant			0.69
No	69	26	
Yes	37	19	
Unknown	20	9	
Splenectomy			0.42
No	115	49	
Yes	8	5	
Missing	3	0	
N lines therapy pre-transplant, median(range)	3 (1–5)	3 (1–5)	0.98
Disease status at transplant			0.96
CR/PR/nPR	58	24	
Stable/progressive	62	27	
Unknown/untreated/not evaluable	6	3	
Refractory to prior therapy			0.74

Variable	TBI	CT	p-value
No	21	10	
Yes	79	36	
Unknown/missing	5	1	
Fludarabine refractory			0.80
No	57	23	
Yes	57	27	
Missing	12	4	
Transplant related			
Interval from diagnosis to transplant, median (range), months	42 (2–223)	41 (4–198)	0.47
Donor-recipient sex-match			0.48
M-M	42	25	
F-F	13	3	
M-F	26	10	
F-M	44	16	
Missing	1	0	
Donor-recipient CMV match			0.57
D(−)/R(−)	31	15	
D(+)/R(+)	57	25	
D(+)/R(−)	13	5	
D(−)/R(+)	24	7	
Missing	1	2	
Graft source			0.006
Bone marrow	63	15	
Blood	63	39	
Donor age, median(range), years	47 (13–66)	45 (24–67)	0.70
ATG			<0.001
Yes	0	8	
No	125	46	
Missing	1	0	
GvHD prophylaxis			0.24
Tacrolimus + methotrexate +/− other	13	11	
Tacrolimus +/− other	8	5	
Cyclosporine + methotrexate +/− other	80	32	
Cyclosporine +/− other	20	4	
Missing	5	2	
Year of transplant			0.02
1995–2000	100	34	
2001–2007	26	20	
Median follow-up of survivors, range, months	130 (3–175)	56 (3–135)	

Table 2

Causes of Death

Variable	TBI	CT
N deaths	81	33
Causes		
CLL	21	9
GvHD	11	3
ARDS	4	0
Infection	18	3
Organ failure	11	9
Graft-failure	2	0
Hemorrhage	2	3
Interstitial pneumonitis	1	0
Other	2	3
Secondary malignancy	4	0
Thromboembolic disease	0	1
Veno-occlusive disease	2	2
Missing	3	0

Table 3

Multivariate Analysis

Outcomes	RR	p-value	95% CI	N
Neutrophil recovery				
TBI	1			123
CT	0.64	0.63	0.10–3.93	53
Acute GvHD ≥grade-2				
TBI	1			123
CT	0.96	0.86	0.60–1.54	52
Chronic GvHD				
TBI	1			112
CT	0.88	0.65	0.52–1.51	52
Relapse				
TBI	1			123
CT	1.49	0.30	0.70–3.18	53
TRM				
TBI	1			123
CT	1.28	0.30	0.80–2.05	53
PFS				
TBI	1			123
CT	1.33	0.16	0.90–1.99	53
Survival				
TBI	1			126
CT	1.34	0.161	0.89–2.02	54