Biol Blood Marrow Transplant 20 (2014) 421-434

Brief Articles

Does Total Body Irradiation Conditioning Improve Outcomes of Myeloablative Human Leukocyte Antigen–Identical Sibling Transplantations for Chronic Lymphocytic Leukemia?

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Article history:
Received 16 September 2013
Accepted 29 November 2013

Key Words:
Chronic lymphocytic leukemia
Total body irradiation
Conditioning
Myeloablative

A B S T R A C T

An allogeneic hematopoietic cell transplantation from an HLA-identical donor after high-dose (myeloablative) pretransplantation conditioning is an effective therapy for some people with chronic lymphocytic leukemia (CLL). Because CLL is a highly radiosensitive cancer, we hypothesized that 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), who received transplants from an HLA-identical sibling donor between 1995 and 2007 and reported to the Center for International Blood & Marrow Transplant Research. At 5 years, treatment-related mortality was 48% (95% confidence interval [CI], 39% to 57%) versus 50% (95% CI, 36% to 64%); P = NS. Relapse rates were 17% (95% CI, 11% to 25%) versus 22% (95% CI, 11% to 35%); P = NS. Five-year progression-free survival and overall survival were 34% (95% CI, 26% to 43%) versus 28% (95% CI, 15% to 42%); P = NS and 42% (95% CI, 33% to 51%) versus 33% (95% CI, 19% to 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 transplantation outcomes between myeloablative TBI and chemotherapy pretransplantation conditioning in persons with CLL.

INTRODUCTION

Hematopoietic cell transplantation from a human leukocyte antigen (HLA)-identical sibling is an 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,

Financial disclosure: See Acknowledgments on page 424.

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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.11.032

Table 1
Subject-, Disease- and Transplantation-Related Variables

Variable	TBI	CT	*P* Value
Subject-related			
Subjects, n	126	54	
Centers, n	65	24	
Age, median (range), yr	48 (24-64)	49 (27-62)	.38
Gender			
Male	86	41	.30
Karnofsky score before transplantation			.41
<90%	41	19	
≥90%	81	35	
Missing	4	0	
Disease-related			
Rai stage at diagnosis			.19
Early Rai stages	83	29	
Late Rai stages	24	11	
Missing	19	14	
Rai stage before transplantation			.46
Early	73	29	
Advanced	41	22	
Missing	12	3	
Constitutional-symptoms at diagnosis			.63
Absent	76	34	
Present	26	8	
Unknown	24	12	
Elevated LDH at transplantation			.69
No	69	26	
Yes	37	19	
Unknown	20	9	
Splenectomy			.42
No	115	49	
Yes	8	5	
Missing	3	0	
Lines therapy before transplantation, median (range), n	3 (1-5)	3 (1-5)	.98
Disease status at transplantation			.96
CR/PR/nPR	58	24	
Stable/progressive	62	27	
Unknown/untreated/not evaluable	6	3	
Refractory to prior therapy			.74
No	21	10	
Yes	79	36	
Unknown/missing	5	1	
Fludarabine refractory			.80
No	57	23	
Yes	57	27	
Missing	12	4	
Transplantation related			
Interval from diagnosis to transplantation, median (range), mo	42 (2-223)	41 (4-198)	.47
Donor-recipient sex-match			.48
M-M	42	25	
F-F	13	3	
M-F	26	10	
F-M	44	16	
Missing	1	0	
Donor-recipient CMV match			.57
D(−)/R(−)	31	15	
D(+)/R(+)	57	25	
D(+)/R(−)	13	5	
D(−)/R(+)	24	7	
Missing	1	2	
Graft source			.006
Bone marrow	63	15	
Blood	63	39	
Donor age, median (range), yr	47 (13-66)	45 (24-67)	.70
ATG			<.001
Yes	0	8	
No	125	46	
Missing	1	0	
GVHD prophylaxis			.24
Tacrolimus + methotrexate +/− other	13	11	
Tacrolimus +/− other	8	5	
Cyclosporine + methotrexate +/− other	80	32	
Cyclosporine +/− other	20	4	
Missing	5	2	
Year of transplantation			.02
1995-2000	100	34	
2001-2007	26	20	
Follow-up of survivors, median (range), mo	130 (3-175)	56 (3-135)	

(*continued on next page*)

Table 1
(*continued*)

TBI indicates total body irradiation; CT, chemotherapy; LDH, lactate hydrogenase; CR, complete remission; PR, partial remission; nPR, nearly partial remission; M, male; F, female; CMV, cytomegalovirus; ATG, antithymocyte globulin; GVHD, graft-versus-host disease.

data from transplantations 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 transplantation outcomes of these two conditioning regimens in subjects reported to the Center for International Blood & Marrow Transplant Research (CIBMTR).

METHODS

Data Sources

The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. 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

One hundred eighty patients with CLL (Richter's transformation and prolymphocytic leukemia were excluded) who underwent a conventional myeloablative (no reduced-intensity) allogeneic transplantation from an HLA-identical sibling between 1995 and 2007 were included. This population was extracted from an initially larger cohort of 1260 subjects reported to the CIBMTR. Patients who received unrelated donor transplants were excluded because of too many missing pieces of data, leaving us with 619 subjects. Further exclusions included subjects with 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 those who received 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 transplantation [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