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HLA-MATCHED SIBLING HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR FANCONI ANEMIA: COMPARISON OF IRRADIATION AND NON-IRRADIATION CONTAINING CONDITIONING REGIMENS

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Abstract

Related to the underlying DNA repair defect that is the hallmark of Fanconi anemia (FA), preparatory regimen related toxicities have been obstacles to hematopoietic cell transplantation (HCT). In an attempt to decrease the risk and severity of regimen-related toxicities, non-irradiation regimens have been explored. The aim of this study is to compare outcomes after irradiation and non-irradiation regimens in 148 FA patients and identify risk factors impacting upon HCT outcomes. Hematopoietic recovery, acute and chronic graft-versus-host disease and mortality were similar after irradiation and non-irradiation regimens. In both groups recipient aged >10 years, prior use of androgens and cytomegalovirus seropositivity in either the donor or recipient were associated with higher mortality. With median follow ups >5 years, the 5-year probability of overall survival, adjusted for factors impacting overall mortality was 78% and 81% after irradiation and non-irradiation regimens, p=0.61. In view of the high risk of cancer and other radiation related effects on growth and development, these results support the use of non-irradiation preparatory regimens. As the peak time for developing

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solid tumors after HCT is 8–9 years, longer follow up is required before definitive statements can be made regarding the impact of non-irradiation regimens on cancer risk.

Key words or short phrases

Fanconi anemia; matched sibling donor; conditioning regimen; survival; graft versus host disease

Introduction

Fanconi anemia (FA) is characterized by congenital malformations, progressive marrow failure and marked predisposition to leukemia, myelodysplasia and epithelial malignancies (1–7). Hematological abnormalities occur in almost all patients with FA at a median age of 7 years (4,5). Allogeneic hematopoietic cell transplantation (HCT) from an HLA compatible family member or unrelated donor is currently the only way to restore normal hematopoiesis (8–10) Overall survival rates of approximately 80% are reported after HLA-matched sibling donor transplantation using cyclophosphamide and limited field irradiation (11). Yet, regimen-related toxicities such as growth retardation, acute and chronic graft-versus-host disease (GVHD) and epithelioid malignancies remain major challenges for these patients (8,11–13). While it is not anticipated that the risks of epithelioid cancers of the head and neck and the urogenital tract will be eliminated, as the risks are high in FA patients not treated by HCT, elimination of radiation from the preparatory regimen may not only minimize the impact of HCT on risk of cancer but also reduce known radiation effects on growth and development. For this reason, a number of groups have explored conditioning regimens that do not contain irradiation (11, 14–17). These reports are limited in numbers of patients studied. In this report we compare the early outcomes using non-irradiation containing conditioning regimens (n=71) to outcomes of regimens with irradiation (n=77) for FA patients transplanted from HLA-matched siblings.

Material and Methods

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR) and the National Marrow Donor Program that comprise of a voluntary working group of over 400 transplant centers worldwide that contribute data on consecutive allogeneic hematopoietic stem cell transplants to a Statistical Center at the Medical College of Wisconsin in Milwaukee. Participating centers register all transplantations consecutively. Patients are followed longitudinally, with yearly follow-up. The CIBMTR collects data at two levels: Registration and Research. Registration data include disease type, age, sex, pre-transplant disease stage and chemotherapy-responsiveness, date of diagnosis, graft type, conditioning regimen, GVHD prophylaxis, post-transplant disease status and survival, development of a new malignancy and cause of death. Research data are collected on selected subsets of registered patients and includes comprehensive pre- and post-transplant clinical information. Computerized checks for errors, physician reviews of submitted data and on-site audits of participating centers ensure the quality of data.

Eligibility criteria

One hundred and forty eight patients receiving their first HLA-matched sibling bone marrow transplant for FA, between 1991 and 2001 and reported to the CIBMTR were eligible. Seventeen patients who received grafts other than bone marrow from a matched family donor were excluded (11 peripheral blood progenitor cell and 6 umbilical cord blood). Seventy-seven of 148 patients received an irradiation-containing regimen and 71, a non-irradiation

conditioning regimen. Transplantations were performed at 35 centers in 16 countries worldwide.

Endpoints

The primary endpoints were neutrophil and platelet recovery, acute and chronic graft GVHD, and overall survival. Neutrophil recovery was defined as achieving an absolute neutrophil count $\geq 0.5 \times 10^9$/L for three consecutive days. Platelet recovery was defined as achieving a platelet count $\geq 20 \times 10^9$/L, unsupported by transfusions for at least 7 days. Diagnosis of acute and chronic GVHD (18,19) was based on local institutional criteria, with the overall grade of acute GVHD assigned retrospectively by the CIBMTR based on stage of involvement reported for each individual organ. Surviving patients were censored at last follow-up.

Statistical Analysis

Patient-, disease- and transplant-related variables for the two treatment groups were compared using the chi-square statistic for categorical and the Kruskal-Wallis for continuous variables (Table 1). All patients were censored at 5-years for evaluation of post-transplant outcomes. The probability of overall survival was calculated using the Kaplan-Meier estimator (20). Probabilities of neutrophil and platelet recovery and acute and chronic GVHD were calculated using cumulative incidence estimator (21). 95% confidence intervals (CI) were calculated using log transformation. Risk factors associated with overall mortality were examined using Cox proportional hazards regression (22). All models were built using a forward stepwise method with a p-value of ≤ 0.05 to indicate statistical significance. Variables that met the criteria for statistical significance were held in the final model. The variable for conditioning regimen (irradiation vs. non-irradiation conditioning regimens), the main variable of interest was held in all steps of model building regardless of level of significance. Other variables tested include: age at transplantation (≤10 vs. >10 years), performance score (90–100 vs. <90), androgen therapy pre-transplant, physical abnormalities (≤3 vs. >3 sites), time from diagnosis to transplantation (≤18 vs. >18 months), donor-recipient CMV sero status (donor/recipient negative vs. either or both donor/recipient positive) and year of transplant (1991–1995 vs. 1996–2001). We examined for an effect of transplant center on overall survival and found none (23). All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Patient, disease and transplant characteristics

Patient, disease and transplant characteristics were similar between the two treatment groups except that recipients of non-irradiation regimens were more likely to have physical abnormalities in >3 sites and transplants with non-irradiation regimens were likely to be more recent (Table 1). The most frequent indication for transplantation was aplastic anemia (N=134); 8 patients were transplanted for leukemia and 6, for isolated thrombocytopenia. A third of patients in the irradiation group and 24% in the non-irradiation group received androgens prior to transplantation. All patients received bone marrow grafts; none were T-cell depleted. GVHD prophylaxis consisted of cyclosporine for all patients, with short course methotrexate in 75 patients. All except one patient received ≤20 red blood cell transfusions pre-transplant. Total nucleated cell dose was reported in 132 of 148 (89%) patients; approximately a third of patients were infused with grafts $\leq 3.0 \times 10^8$/kg. The median follow-up of surviving patients is 8 years after an irradiation regimen and 5 years after non-irradiation regimens. In order to account for the differential follow up between treatment groups, all patients were censored at 5-years for evaluation of post-transplant outcomes.

Hematopoietic recovery

The median time to neutrophil recovery was 13 days and 17 days after irradiation containing and non-irradiation regimens, respectively. The day-28 probability of neutrophil recovery was similar after irradiation containing and non-irradiation regimens; 94% (95% CI 86–98) and 89% (95% CI 80–96), p=0.35. Two patients failed to achieve neutrophil recovery after irradiation-containing regimens and 3, after non-irradiation regimens. Recovery times were slower in patients who received cyclosporine and short course methotrexate (relative risk [RR] 0.63, 95% CI 0.44–0.91, p=0.01). The day-100 probability of platelet recovery was similar after irradiation containing and non-irradiation regimens; 92% (95% CI 85–97) and 92% (95% CI 84–97). Secondary graft failure rates were low (n=5); 4 cases after irradiation containing regimens (graft failure occurred at 4 months, 15 months [n=2] and 39 months after transplantation) and 1 after a non-irradiation containing regimen and occurred at 9 months.

Graft-versus-host disease

The day-100 probabilities of acute grade 2–4 GVHD were similar after irradiation containing and non-irradiation regimens, 23% (95% CI 15–33) and 21% (95% CI 13–31), p=0.74, respectively. The corresponding probabilities of grades 3–4 acute GVHD were 6% (95% CI 2–13) and 10% (95% CI 4–18), p=0.46. The 5-year probabilities of chronic GVHD were 18% (95% CI 10–28) and 24% (95% CI 14–35), after irradiation containing and non-irradiation regimens, respectively (p=0.40).

Overall mortality

Risks of mortality were similar after irradiation containing and non-irradiation regimens, adjusted for other factors associated with mortality (Table 2). Older patient age (>10 years), use of androgens pre-transplant and cytomegalovirus seropositivity in the donor and/or recipient were associated with higher mortality risks. The 5-year probabilities of overall survival adjusted for the above mentioned significant factors were 78% (95% CI 67–85) and 81% (95% CI 71–88) after irradiation containing and non-irradiation regimens, respectively (p=0.61). Mortality rates were higher in patients with acute and chronic GVHD (RR 3.47, 95% CI 1.64–7.33, p=0.001 and RR 4.06, 95% CI 1.63–10.12, p=0.003), respectively.

Four patients developed malignant neoplasm (squamous cell carcinoma). These patients were transplanted at 7, 10, 14 and 20 years of age. Two patients received irradiation-containing regimens and developed squamous cell carcinoma at 55 and 101 months after HCT. The remaining two patients received non-radiation regimens and developed squamous cell carcinoma at 58 and 60 months, post-HCT. One patient had a history of acute GVHD and two patients, chronic GVHD. Only one patient received azathioprine for treatment of chronic GVHD.

Thirty-one patients died, 16 after irradiation-containing regimens and 15, after non-irradiation conditioning regimens. Most deaths occurred within 2 years after transplantation; 14 after irradiation containing regimens and 12, after non-irradiation regimens. **Causes of death did not differ by conditioning regimen. The most common causes of death within the first 2 years after transplantation were infections (n=6), organ failure (n=6) and GVHD (n=5)**. Death after the first 2 years after transplantation were infections (n=2), hemorrhage (n=1) and squamous cell carcinoma of tongue (n=1) (Table 3).

Discussion

Transplantation of hematopoietic stem cells from a HLA-matched sibling, when such a donor is available is the treatment of choice for the bone marrow failure syndrome that characterizes FA. The introduction of low dose alkylating agents with limited field irradiation led to

significant improvements in survival (8,11). FA patients are predisposed to developing epitheliod carcinomas after the age of 20 years regardless of whether they undergo transplantation (24). Deeg and colleagues (12) identified irradiation-containing conditioning regimens as a risk factor for post-transplant malignancy in patients with FA. Consequently, there has been increasing interest in the use of non-irradiation containing regimens for FA particularly if an HLA-matched sibling donor is available. In this study we have explored outcomes in a relatively large group of recipients of HLA-matched sibling transplants using irradiation and non-irradiation conditioning regimens.

The current report identified three factors associated with higher mortality: use of androgens pre-transplant, age at transplant (>10 years) and CMV seropositivity in the donor and/or recipient. Use of androgens pre-transplant for marrow aplasia is controversial. While oxymetholone and other androgens have been reported to improve blood counts in approximately 50% of patients, side effects are substantial, including masculinzation, **peliosis hepatitis** and hepatic adenoma. Furthermore, the effectiveness of androgen treatment is of limited duration (1). For these reasons and the fact that there is a high probability of survival after an HLA matched sibling transplant, androgens are generally avoided when a HLA-matched sibling is available.

Age at transplantation is also an adverse risk factor (9,11,25). While it is not recommended that transplant be performed before marrow failure, less toxic preparatory therapies and alternate approaches for preventing GVHD are needed to reduce regimen related toxicities. Similarly, CMV seropositivity in the donor and/or recipient and its adverse effect on mortality has also been reported by others for FA (9,26). While deaths are not often directly due to CMV, this may be a surrogate marker for delayed immune recovery. New strategies for reducing the period of immunodeficiency are required.

Other reported risk factors include transfusion exposure, and presence of >3 congenital malformations. Higher mortality in recipients of over 20 pre-transplant transfusions has been previously reported (8,25). In the current report, all patients but one received ≤20 red blood transfusions and approximately 80% received ≤10 or fewer red blood cell transfusions indicating that patients with HLA-matched siblings are referred for transplantation in a timelier manner since the publication of the above mentioned reports. Though we were unable to find an association between numbers of red blood cells transfused pre-transplant (≤10 versus >10), the current analysis may not be sufficiently powered to defect a meaningful difference between the groups. We also examined the impact of congenital malformations and found none. This contrasts with an earlier EBMT report where mortality rates were higher in patients with 3 or more congenital abnormalities after unrelated donor HCT (24) and from the Hopital Saint Louis where acute GVHD rates were higher in patients with urogenital malformations after HLA-matched sibling HCT (13).

We observed similar rates of acute and chronic GVHD after radiation and non-irradiation regimens. Acute GVHD rates after irradiation regimens in this report was 23% and lower to acute GVHD rates of 62% observed at Hopital Saint Louis where the conditioning regimen contained limited field irradiation (13). The lower rate in this report may be explained by the use of anti-thymocyte globulin in over 60% of patients who received limited filed irradiation. We were unable to identify risk factors associated with acute or chronic GVHD in this analysis. This is not unexpected given the relatively small numbers of patients and few events. However, the proportion of patients with acute or chronic GVHD was lower in patients who received anti-thymocyte globulin (data not shown). The occurrence of acute or chronic GVHD had an adverse impact on mortality confirming the observations of others that GVHD is a major limitation to a successful outcome after transplantation in FA.

With 5-year overall survival rates of approximately 80% physicians must be encouraged to refer FA patients with a HLA-matched sibling for transplantation as soon as aplasia develops. Avoidance of androgens and minimal transfusion prior to transplantation can only further improve the overall survival rate. GVHD remains a limitation; mortality rates are higher as are risks of squamous cell carcinoma. The use of ATG may have lowered GVHD rates but the duration of immune suppression is longer and the patient subject to opportunistic infections and consequent morbidity and mortality. As the peak onset for malignant neoplasms tend to occur later than 5 years (the median follow up of this cohort) after HCT longer follow-up of is required to determine whether its prevalence after non-irradiation regimens will remain similar to that after radiation regimens as observed.

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Table 1

Patient, disease and transplant characteristics of FA patients by conditioning regimen received for HLA-matched sibling transplants

Variables	Conditioning regimen				P-value
	Irradiation		Non-irradiation		
	N	N (%)	N	N (%)	
Number of patients		77		71	
Number of centers		23		12	
Age at transplant	77		71		0.67
≤10y		45 (58)		39 (55)	
11–20y		32 (42)		32 (45)	
Male	77	45 (58)	71	34 (48)	0.20
Performance score pre-transplant	77		71		0.07
<90		13 (17)		21 (30)	
≥90		63 (82)		49 (69)	
Unknown		*1* (*1*)		*1* (*1*)	
Pre-transplant therapy					
Androgens	77		71		0.21
Yes		26 (34)		17 (24)	
No		49 (64)		51 (72)	
Unknown		*2* (*3*)		*3* (*4*)	
Physical abnormalities	77		71		0.01
≤3 sites		41 (53)		27 (38)	
>3 sites		26 (34)		42 (59)	
Unknown		*10* (*13*)		*2* (*3*)	
Conditioning regimen[1]	77		71		NA
Radiation containing					
TLI/TAI + Cy + ATG		29 (38)		—	
TBI + Cy ± ATG		20 (26)		—	
TLI/TAI + Cy		28 (36)		—	
Non-radiation containing					
Cy alone		—		45 (63)	
Cy + ATG		—		17 (24)	
Bu + Cy		—		3 (4)	
Fludarabine + Cy[2]		—		6 (9)	
Donor-recipient CMV status	77		71		0.01
Donor +/recipient +		31 (41)		45 (63)	
Donor +/recipient −		11 (14)		7 (10)	
Donor −/recipient +		11 (14)		10 (14)	
Donor −/recipient −		23 (30)		8 (11)	
Unknown		1 (1)		1 (2)	
Year, transplant	77		71		<0.001
1991–1994		45 (58)		23 (32)	
1995–2001		32 (42)		48 (68)	
Median follow-up of survivors, Months	77	96 (9 – 153)	71	58 (16 – 143)	

[1] Regimen doses are:

- Limited field irradiation + cylocphosphamide ± anti-thymocyte globulin
  - Limited field irradiation dose: 400–600 cGy
  - Cyclophosphamide dose: 20 mg/kg

- Total body irradiation+ cyclophosphamide ± anti-thymocyte globulin
  - Total body irradiation dose: 500 cGY
  - Cylophosphamide dose: 20–60 mg/kg
- Cyclophosphamide ± anti-thymocyte globulin
  - Cyclophosphamide dose: 60–200 mg/kg
- Busulfan + cyclophosphamide
  - Busulfan dose: 8 mg/kg
  - Cyclophosphamide dose: 20–80 mg/kg
- Fludarabine + cyclophosphamide
  - Fludarabine dose: 120–180 mg/m^2
  - Cyclophosphamide dose: 20–80 mg/kg

[2]Regimen includes:

- Fludarabine + cyclophosphamide + anti-thymocyte globulin (n=4); Fludarabine + cyclophosphamide + Campath (n=2)

Table 2

Multivariate analysis showing risks of overall mortality after HLA-matched sibling transplants in patients with FA

Variables	N	Relative Risk (95% Confidence Interval)	P-value
Main effect:			
Radiation	74	1.00	
Non-radiation	68	0.96 (0.46 – 1.99)	0.904
Other significant covariates:			
Age at transplant:			
≤10 years	79	1.00	
>10 years	63	4.24 (1.81 – 9.93)	<0.001
Androgen therapy:			
No	100	1.00	
Yes	42	2.62 (1.26 – 5.44)	0.008
Donor-recipient CMV status:			
Both negative	31	1.00	
Either or both positive	111	4.67 (1.08 – 20.11)	0.039

Table 3

Causes of death

Causes of death	Within 2 years of BMT		Beyond 2 years from BMT	
	N eval	N	N eval	N
Number of patients	26		5	
Graft failure		**3**		0
Infection		6		2
GVHD		**5**		0
Organ failure		**6**		0
Hemorrhage		2		1
Squamous cell carcinoma		0		1
Other		4		1