Clinical Communications

Allogeneic stem cell transplantation in adolescents and young adults with primary immunodeficiencies

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Clinical Implications

- In this study, outcome after allogeneic hematopoietic stem cell transplantation for adolescents and young adults with primary immunodeficiency diseases was excellent and comparable to that in pediatric patients.
- In the complex scenario determining whether an adolescent and young adult patient with primary immunodeficiency diseases should undergo hematopoietic stem cell transplantation, age should not be the key deciding factor.

TO THE EDITOR:

Adolescents and young adults (AYAs) have gained increasing attention from medical care providers for their specific medical and psychosocial needs that should be addressed by a specialized interdisciplinary team.[1] If treated for acute leukemia with chemotherapy or allogeneic hematopoietic stem cell transplantation (HSCT), these patients have long had an inferior outcome compared with pediatric patients.[2,3] HSCT is the standard of care for children with many primary immunodeficiency diseases (PIDs).

AYAs with the same PIDs who were previously not considered candidates for HSCT or who have been diagnosed later in life because of less severe disease manifestations are increasingly diagnosed and sometimes referred for HSCT or are referring themselves to explore the possibilities of a potentially curative treatment.[4] The outcome of HSCT in this group of patients is often presumed to be inferior to that in their pediatric counterparts because of increased transplant-related morbidity and mortality, but reliable data in PIDs are lacking. In a prospective study with reduced-intensity conditioning, Gungor et al[5] demonstrated that young adults with chronic granulomatous disease (CGD) can be cured with encouraging survival and acceptable toxicity,[5] whereas in a study on patients with severe complications of common variable immunodeficiency aged 8 to 50 years, the outcome after HSCT was poor, with only 48% overall survival, mostly due to graft versus host disease (GvHD)-associated mortality.[6]

To investigate the HSCT outcome in AYAs with PIDs compared with pediatric patients, we retrospectively compared the 2 groups at a single center.

Eighteen AYA patients with a median age of 18.5 years (15.0-22.1) and 43 pediatric patients with a median age of 4.8 years (0.3-14.8) at the time of HSCT were identified and consecutively included into this analysis. AYA patients were more likely to be transplanted from an unrelated donor (16 of 18 [89%]) than the pediatric patients (21 of 43 [49%]; $P = .003$). The underlying genetic diagnoses as well as patient and transplant characteristics are detailed in Table I.

After a median follow-up of 5.0 (2.0-8.0) and 4.8 (2.2-9.6) years, overall survival was 94% and 96% ($P = .88$) in the AYA and pediatric cohorts, respectively, while event-free survival was 94% and 86% ($P = .37$; Figure 1, *A* and *B*). Complete (>90%) donor chimerism was documented in 17 of 18 (94%) AYAs and 34 of 43 (79%) pediatric patients at last follow-up ($P = .14$). Four pediatric patients rejected their graft between 1 and 12 months after HSCT and experienced recurrence of their original disease. Two of them were successfully retransplanted from different donors. One AYA patient died from disseminated adenovirus disease on day +105 after HSCT and 2 pediatric patients died from bacterial sepsis (d+552) and metapneumovirus infection (d+1769), respectively.

No patient experienced grade III or IV acute GvHD in either group. Significantly more patients in the AYA cohort (11 of 18 [61%]) experienced acute GvHD of any grade compared with the pediatric patient group (9 of 43 [21%]; $P = .002$) but it was mostly overall grade I (9 of 11 patients) and restricted to the skin in all (Figure 1, *C* and *D*; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Chronic GvHD was also more frequent in the AYA group (4 of 18 [22%] vs 1 of 43 [2%]; $P = .01$) but did not exceed the National Institutes of Health severity score of 1 and resolved in all patients (Figure 1, *E*). No patient continues to be on immunosuppressive therapy in either cohort. All HSCT outcome data are summarized in Table E1.

We analyzed the influence of pre-HSCT complications such as active infection, active inflammation, and malignancy on outcome. As expected, the AYA patients had a higher pre-HSCT risk profile, with 11 of 18 patients (61%) with at least 1 pretransplant risk factor, which was not significantly more than in the pediatric group (17 of 43 [40%]; $P = .12$). The presence of risk factors did not translate into worse overall or event-free survival (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

These data support the notion that AYAs with PIDs should undergo evaluation for HSCT if their underlying disease and individual clinical course suggest poor long-term outcome with respect to survival, organ function, and quality of life. However, natural disease outcome data for most PIDs are lacking. One notable exception may be CGD, where long-term survival data stemming from registries as well as a quality-of-life analysis in patients with or without HSCT have been published.[7] In CGD, earlier reports suggested a high rate of complications and poor outcome in young adults undergoing HSCT, but a more recent study incorporating 32% AYAs and using a submyeloablative reduced-toxicity conditioning regimen demonstrated improved survival in this age group.[5]

Most of the patients in our study were transplanted using protocols recommended by the Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation and European Society for Immunodeficiencies.[8] The results from our study indicate that AYA patients with PIDs have surprisingly

TABLE I. Patients and transplant characteristics

Characteristic	AYA	PED	*P* (where applicable)
n	18	43	
Sex: F/M	8/10	17/26	.72
Median age at transplant (y) (range)	18.5 (15.0-22.1)	4.8 (0.3-14.8)	
Diagnosis (n)	CGD (6) DOCK8 (2) GATA2 (2) Undefined CID (1) CTLA4, FHLH, NBS, RAG1, JAGN1, WAS, XLP (1 each)	CGD (8) FHLH (6) WAS (6) Undefined CID (4) DOCK8 (3) IL-10R (2) XIAP (2) ADA, CD40L, GATA2, IKBA, IPEX, LIG4, MHCII, NBS, ORAI1, RAG1, RAG2, TTC7A (1 each)	
Number of pretransplant risk factors, n (%)			
0	7 (39)	26 (60)	.12
1	10 (56)	13 (30)	.06
2	1 (6)	4 (9)	.63
Type of risk factor			
Active infection (n)	MRSA bacteremia (1)	Aspergillosis (1) CMV (1) BCG (1) RSV (1)	
Active inflammation (n)	IBD (3) Chronic pulmonary disease (1) Severe eczema (1)	IBD (7) Chronic pulmonary disease (2) PAP (1) Severe eczema (2) GvHD, transfusion associated (1)	
Malignancy (n)	6 (33%) MDS (2) AML (1) NHL (2) HD (1)	4 (9%) MDS (2) NHL (2)	**.02***
Mean Lansky/Karnofsky score at HSCT (range)	92.2% (80-100)	92.3% (70-100)	
Donor, n (%)			
MSD/MFD	2 (11)	15 (35)	.06
10/10 MUD	5 (28)	11 (26)	**.003***
9/10 MUD	11 (61)	10 (23)	
MMFD	0 (0)	7 (16)	.07
Stem cell source, n (%)			
Bone marrow	14 (78)	36 (84)	.58
PBSC	4 (22)	7 (16)	.58
Conditioning, n (%)*			
Full BuCy	2 (11)	4 (9)	.35
Full BuFlu	1 (6)	8 (19)	
Sub BuFlu	7 (39)	6 (14)	.09
Min BuFlu	—	2 (5)	
FluMel ± TT	1 (6)	10 (23)	.10
TreoFlu ± TT	7 (39)	13 (30)	.51
Serotherapy (ATG or alemtuzumab)	18 (100)	41 (95)	.35
GvHD prophylaxis, n (%)			
CSA MMF	13 (72)	29 (67)	.71
CSA MTX	5 (28)	8 (19)	.43

(continued)

little transplant-associated mortality and GvHD if using these reduced-toxicity conditioning regimens based on fludarabine and either treosulfan or targeted busulfan with serotherapy. GvHD has been reported to occur more frequently in AYAs.[9] In our cohort, both acute and chronic GvHD were significantly more frequent in AYA patients. However, the complete absence of