Fertility After Allogeneic Hematopoietic Stem Cell Transplantation: A 23-Year Review From A Tertiary Hospital

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ABSTARCAT

Infertility is a major late side effect after allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, healthy pregnancies and births were reported previously. We retrospectively evaluated the fertility of 107 adult patients who underwent Allo-HSCT (median age: 32.3) between 1989-2012 at our center and survived 2 years or more after transplantation. From totally 29 pregnancies (21 partners of male patients vs 8 female patients), 6 of the female patients (14%) and 20 of the male patients (45%), had a child after Allo-HSCT. The benign nature of the initial diagnosis, lack of chemotherapy regimen before transplantation, early age and no relapse of the primary disease contribute to fertility in our study. No relation was detected between the myeloablative conditioning regimen, radiotherapy prior to Allo-HSCT, TBI usage and frequency, and development of acute and chronic GVHD with infertility.

Keywords: Allogeneic stem cell transplantation, Fertility

ÖZET

Allojeneik Hematopoietik Kök Hücre Nakli Sonrasinda Fertilite: Üçüncü Basamak Hastanenin 23 Yıllık Veri Derlemesi- Allojeneik kök hücre nakli (AKHN) sonrası en önemli uzun dönem yan etkilerden birisi infertilitedir. Fakat, daha önceki çalışmalarda sağlıklı gebelikler ve doğumlar bildirilmiştir. 1989-2012 yılları arasında merkezimizde AKHN yapılmış ve transplantasyon sonrası 2 yıl ve üzeri yaşayan 107 erişkin hasta (ortanca yaş: 32,3) retrospektif olarak değerlendirilmiştir. 29 gebelikten (21 erkek hastaların eşlerinden, 8 kadın hasta), 6 kadın hasta (%14) ve 20 erkek hastanın eşi (%45) AKHN sonrasında çocuk sahibi olmuştur. Tanı anında benign karakterde hastalık, transplantasyon öncesi kemoterapi almamış olmak, erken yaş, primer hastalığın nüksünün olmaması fertilite ile ilişkili olarak bulunmuştur. Myeloablatif hazırlık rejimi, AKHN öncesi radyoterapi, TBI kullanımı ve sıklığı, akut veya kronik graft versus host hastalığı fertilite ile ilişkili değildir.

Anahtar Kelimeler: Allojeneik kök hücre nakli, Fertilite

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has become the gold standard curative approach for a variety of hematological disorders. The overall survival and cure rates of patients with hematological malignancies have improved dramatically with modern antitumor modalities including allo-HSCT.

Today, attention is focused on late transplant-related complications, including those that are life-threatening but also those that may worsen patient quality of life.[1] Loss of fertility affects quality of life in transplant survivors. Infertility is an essential issue for healthcare professionals dealing with cancer patients. Borgmann-Staudt et al. reported that impaired fertility was observed 3-12 years after the treatment in 69% of male patients and 83% of female patients who received allo-HSCT at an early age.[2] High doses of alkylating agents and/or total body irradiation (TBI) as well as older age in women at the time of transplant were found to be related to gonadal dysfunction and infertility.[3] Recovery of fertility after HSCT therapy has been reported in both sexes; in males the rate of spermatogenesis may increase with time.[4] Successful pregnancies after HCST have been reported in previous studies.[5] In this study, we investigated the pregnancy outcomes and factors related to infertility in our patients after allo-HSCT.

PATIENTS AND METHODS

We retrospectively evaluated the fertility of 107 eligible patients who underwent allo-HSCT and survived 2 years or more after the transplantation between 1989-2012 in the Department of Adult Hematology at Ankara University. All patients gave their written informed consent for participation in the study, which was approved by the local Ethical Committee. Patients and transplant data were collected using electronic clinical records. Our clinical records consist of disease status, treatment lines and types, conditioning regimens, graft versus host disease (GVHD) state, complications and fertility. Data on ovarian function and fertility was evaluated in female by serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) measured at day 2 or 3 of the cycle in patients with spontaneous menses or during amenorrhea in others. In male patients who wanted to have a child from their partner the serum levels of FSH, LH and testosterone and spermiogram analysis were done. Detailed data regarding pregnancies and complications before or after allo-HSCT were collected from the patient or patient's spouse by phone calls and/or clinical visits. The stem cell sources for transplants were bone marrow (32.7%) or peripheral blood (61.3%). Donors were HLA-matched related (96.3%) or HLA-matched or mismatch unrelated (2.7%). Myeloablative (92.5%) or reduced intensity (7.5%) conditioning regimens were preferred due to patient status and underlying disease. All patients received prophylaxis for GVHD and infections. None of the patients or partners of the patients included in this study were using any of the contraception method.

Statistical Analysis

All of the numerical values were given as the median with the distribution range. We used the Pearson chi-square test or Fisher exact test to compare categorical variable. $P< 0.05$ was considered statistically significant.

RESULTS

In 107 patients (44 Female/63 Male), the median age at the time of study participation was 41.2 (range, 22-59 years), whereas the median age at allo-HSCT was 32.3 (range, 16-45 years). Seventy-one of 107 patients (66%) were 30 years or older at the time of allo-HSCT. The median length of follow-up time after allo-HSCT was 86 months (range, 28-237 months). The patient characteristics are shown in Table 1. Thirteen of the 107 patients had no history of chemotherapy or radiotherapy prior to allo-HSCT. Only 3 patients had received radiotherapy before allo-HSCT apart from what was contained in the conditioning regimen. A myeloablative conditioning regimen was preferred in 40 of the female patients (91%) and 59 of the male patients(94%). The most common site of acute GVHD was skin in women (41%), whereas both skin and gastrointestinal system (48%) complications were observed in men. Chronic GVHD with liver involvement was the most common oc-

Table 1. Patient Characteristics

Variables	Female (n= 44)	Male (n= 63)	P
Age			
Median age at Allo-HSCT, years (range)	32.3 (16-45 years)	32.4 (16-45 years)	> 0.05
Age ≥ 30 at AlloHSCT, n (%)	30 (68%)	41 (65%)	
Diagnosis, n (%)			
Acute leukemia	21 (48%)	36(57%)	> 0.05
Chronic myeloproliferative disease	12 (27%)	20 (32%)	
Bone marrow failure	8 (18%)	2 (0.3%)	
Other	3 (0.7%)	5 (0.8%)	
Donor, n (%)			
HLA-matched relative	41 (93. 2%)	62 (98.4%)	> 0.05
HLA-matched or mismatched non-relative	3 (6.8%)	1 (2.6%)	
Stem Cell Source, n (%)			
Bone Marrow	14 (32%)	21 (34%)	> 0.05
Peripheral Blood	30 (68%)	42 (66%)	
Conditioning Regimen, n (%)			
Cyclophosphamide	40 (91%)	58 (92%)	> 0.05
ATG (antithymocyte globulin)	11 (25%)	6 (10%)	
Fludarabine	6 (14%)	7 (11%)	
Busulphan	35 (80%)	47 (75%)	
TBI (total body irradiation)	3 (7%)	10 (16%)	
Development of GVHD, n (%)			
Acute GVHD	15 (34%)	25 (40%)	> 0.05
Chronic GVHD	25 (57%)	39 (62%)	
Relapse of primary disease after Allo-HSCT, n (%)	11 (25%)	20 (32%)	> 0.05

currence in both females (38%) and males (32%). Median time to relapse of the primary hematological disease after allo-HCST was 32 months. During follow-up, 21 patients died of primary disease relapse.

Median age, diagnosis, donor type, stem cell source, conditioning regimen, frequencies of acute or chronic GVHD and the incidence of relapse were similar in the male and female groups (p> 0.05) (Table 1).

Fertility Status Prior to and After Transplantation

Thirty patients (28%) in our cohort had a child, whereas 19 patients/patient partners (18%) had a history of pregnancy complications prior to the transplantation. Seventy-nine patients or their spouses (74%) reported using at least one birth control method during the pre-transplant period, most commonly an intra-uterine device. None of the patients/partners of patiens were using any contraception method post-tranplant. During the pre-transplant period, there were 14 spontaneous abor-

Table 2. Clinical characteristics and pregnancy complications of survivors reporting pregnancies after allo-HSCT

Variables		Female (n= 6)	Male (n= 20)
Pregnancy outcomes, n (%)			
Live births	6 (100%)	18 (90%)	
Miscarriage	1 (17%)	8 (30%)	
Stillbirth	1 (17%)	1 (5%)	
Pregnancy complications, n (%)			
Preeclampsia	1 (17%)	-	
Gestational diabetes	1 (17%)	1 (5%)	
Gestational hypertension	-	1 (5%)	
Mean time to pregnancy, months (range)	63 (8-108)	68 (4-144)	
Median Age at first post-HCT pregnancy, years (range)	30 (22-38)	32 (22-48)	
Diagnosis, n (%)			
Acute leukemia	1 (17%)	9 (45%)	
Chronic myeloproliferative disease	1 (17%)	10 (50%)	
Bone marrow failure	4 (66%)	1 (5%)	
Conditioning Regimen, n (%)			
Cyclophosphomide	6 (100%)	20 (100%)	
ATG (antithymocyte globulin)	4 (66%)	1 (5%)	
Fludarabine	1 (17%)	1 (5%)	
Busulphan	2 (34%)	17 (85%)	
TBI (total body irradiation)	-	1 (5%)	

tions. Nine of 44 female patients (20%) had regular menstrual cycles after transplantation. 6/9 patients (66%) were diagnosed with benign hematological diseases. Serum hormonal levels were measured in 19 out of 44 patients. Despite the presence of menstrual cycles in 9 patients, elevated FSH (median 46 IU/L; range 3-87) and LH levels (median 32 IU/L; range 1-62) were detected. Serum FSH, LH and testosterone levels and spermiogram were analyzed in 29 of 63 male patients and resulted within normal range.

A total of 26 (24%) survivors reported 35 post-HSCT conceptions; these included 20 (45%) male survivors and 6 (14%) female survivors (Table 2). 3 of 6 female survivors had spontaneous menstrual cycles. Outcomes of post-HCT conceptions included 24 live births (69%), 9 miscarriages (26%), and 2 stillbirths (5%). All of the female recipients achieved pregnancy without assistance; however, two male patients did have children with in vitro fertilization. The median duration of pregnancy in the female survivors was 37.67 ± 2.07 weeks compared to partners of male survivors at 38.31 ± 1.62 weeks. No preterm deliveries were observed in either group. Cesarean (C/S) and normal delivery rates were equal in frequency in female patients (50%), whereas partners of male patients had more C/S deliveries (55% vs 45%). The median weight of child at birth was 3.10 ± 0.81 kg in female patients and 3.30 ± 0.63 in male patients. A low birth weight child was detected in 1 (17%) female pregnancy and in 6 (33%) pregnancies of partners of male transplant recipients ($p > 0.05$). Two children of partners of male recipients had congenital abnormalities, including 1 dysmorphic ear and 1 cardiac vein anomaly.

All patients who gave birth after allo-HSCT had received transplants from full-match HLA sibling donors or relatives. A myeloablative conditioning regimen was chosen in 25 survivors, and 1 male

Table 3. Comparison of fertile vs infertile patients

Variables, n (%)	Fertile (n= 26)	Infertile (n= 81)	p
Age ≥ 30 at alloHSCT	8 (31%)	59 (73%)	< 0.0001*
Male/Female	20 (77%) /6 (23%)	43 (53%)/38 (47%)	0.032*
Median age, years (range)	40 (23-53)	43 (22-59)	0.02*
Age at diagnosis, years (range)	26.5 (16-39)	35 (16-45)	< 0.0001*
Diagnosis, n (%)			
Acuteleukemia	10 (38%)	47 (58%)	0.025*
Chronic myeloproliferative disease	11 (42%)	21 (26%)	
Bone marrow failure	5 (19%)	5 (6%)	
Other	-	8 (10%)	
Donor type			
Relative/Non-Relative	26 (100%)/-	77 (95%) /4 (5%)	0.57
Pre-transplant therapy, n(%)			
Chemotherapy	20 (77%)	74 (91%)	0.07
Radiotherapy	-	3 (3%)	1.0
Conditioning regimen, n(%)			
ATG (antithymocyte globulin)	5 (19%)	12 (15%)	0.59
Cyclophosphomide	26 (100%)	72 (88%)	0.10
Fludarabine	2 (7%)	11 (14%)	0.73
Busulphan	19 (73%)	63 (77%)	0.06
TBI (total body irradiation)	1 (4%)	12 (15%)	0.18
Relapse after Allo-HSCT	3 (12%)	28 (35%)	0.026 *
Acute GvHD	9 (35%)	31 (38%)	0.74
Chronic GvHD	14 (54%)	50 (62%)	0.48
Stem Cell Source			
Bone Marrow	16 (62%)	10 (12%)	0.001*
Peripheral Blood	10 (38%)	62 (88%)	

* p< 0.05, statistically significant

patient had reduced intensity conditioning. The conditioning regimens were: Busulphan (BU) 3.2 mg/kg/day plus cyclophosphamide (CY) 60 mg/kg/day (73%), cyclophosphamide 50 mg/kg/day plus antithymocyte globulin (ATG) 30mg/kg/day (11%), Fludarabine (Flu) 30 mg/m^2/day plus CY 60mg/kg/day plus ATG 10mg/kg/day (4%), CY 60 mg/kg/day plus TBI 2 x 2 Gy/day (4%), Flu 30 mg/m^2/day plus BU 4 mg/kg/day plus ATG 10 mg/kg/day (4%), CY 60 mg/kg/day (4%). The stem cell source was bone marrow in 4 fertile female patients (66%) and 12 (60%) male patients. Acute/chronic GVHD was detected in 2 (33%)/2 (33%) female survivors and 7 (35%)/12 (60%) male survivors. The partners of 3 of the male recipients (15%) reported pregnancy after disease relapse. Sperm cryopreservation was utilized in only 2 male survivors and ovarian cryopreservation was utilized in 1 female survivor, but attempts for pregnancy were not reported in these patients.

Comparison of Fertile and Unfertile Patients

Comparisons of several parameters between fertile vs unfertile patients are shown in Table 3. Age ≥ 30 at the time of allo-HSCT was associated with increased risk of infertility (31% vs 73%, p< 0.0001). The partners of male patients had more pregnancies than the female patients (77% vs 53%, p= 0.032). The median age at both study participation and diagnosis were found to be statistically higher in the infertile group (40 vs 43, p=0.02; 26.5 vs 35, p< 0.0001). Malignant hematological diseases rather than chronic myeloproliferative disease (CMPD) and bone marrow (BM) failure also had increased risk of infertility (38% vs 55%, p= 0.025). The fertile patients relapsed after allo-HSCT less frequently than the infertile patients (12% vs 35%, p= 0.026). Stem cell source of bone marrow was found to be associated with increased fertility outcome (62% vs 12%, p= 0.001*).

Fertility was not found to be related to donor type, pretransplant chemotherapy or radiotherapy, conditioning regimen including cyclophosphomide, fludarabine, busulphan, TBI or acute/chronic GVHD (p> 0.05).

DISCUSSION

Successful pregnancies have been reported in female HCT patients and female partners of male HCT patients. Salooja et al investigated the pregnancy rates of nearly 38,000 transplant patients (autologous and allogeneic) by sending questionnaires to 199 centers. They reported 312 pregnancies from 232 patients for an overall conception rate of 0.6%. (6). In 2006, Bone Marrow Transplant Survivor Study (BMTSS) reported the pregnancy outcomes of 619 HCT survivors and partners and compared these outcomes with those of the patients' nearest age siblings. There were 54 pregnancies reported from 34 (5.5%) patients (26 female, 8 male) with 46 live births and an overall lower prevalence of conception compared to their siblings. The median age at study participation was 42.6 years (range 23.3-60.4 years), whereas the median age at transplant was 33.3 years (21.0-45.0) (7). In our study, a total of 26 (24%) survivors reported 35 post-HCT conceptions from 107 participants. These included 20 (45%) male survivors and 6 (14%) female survivors. The overall conception rate was higher than in previous studies, which may have occurred because our study contains a homogenous cohort of patients who were truly of child-bearing age and were interested in conceiving children. Consistent with this hypothesis, the median age at both study participation and allo-transplantation was lower than in the previous reports. Younger age is associated with an increased likelihood of fertility recovery.[2] Previous studies indicated that fertility is most frequently preserved in patients receiving a transplant in the young adult age group (15-30 years).[8] This was supported by our study, which showed that age > 30 years at Allo-HSCT was related to increased risk of infertility.

Center for International Blood and Marrow Transplantation Research (CIBMTR) data included 178 pregnancies (83 female, 95 female partners of HCT recipients) with a median age at pregnancy similar to that in our study. In addition, in both women and partners of men receiving myeloablative HCT the median time to pregnancy was 7 years after HCT in the CIBMTR data.[8] We report shorter median time to pregnancy after allo-HCT in partners of male survivors (68.15 months) and female survivors (63.33 months). A partner of one male patient conceived 28 months after allo-HST. These time periods are consistent with the observation that spermatogenesis recovers in 20% to 25% of HCT patients after prolonged follow-up.[4] Longer follow-up is important if fertility is desired.

Central or peripheral gonadal failure are frequent complications of allo-HSCT that cause infertility. The probability of recovery of ovarian function declines by 0.8 per year with increasing age at transplantation.[9] Gonadal failure depends on several factors including the age of the patient, the type of chemotherapy and total body irridation (TBI). The conditioning regimen for HSCT usually consists of TBI with 12-14 Gray (Gy) and chemotherapy with cyclophosphamide (CY), etoposide (VP) or combination of busulfan (BU) and CY.[10] All antineoplastic drugs, especially alkylating agents, have dose-dependent toxic effects on both oocytes and granulosa cells.[11,12] Alkylating agents can damage primordial follicles through apoptotic cell death, resulting in destruction of ovarian reserve.[13] Although BU is considered to be highly gonadotoxic, especially in women, there are conflicting results

and different diagnoses.[10] In men, both alkylating agents and irradiation were found to be gonadotoxic to germ cell epithelium and Leydig cells in the testis.[14] We did not detect a fertility advantage for any specific conditioning regimen or TBI. In fact, only 1 of fertile patients received reduced intensity regimen and 1 received high dose TBI which is not sufficient to detect the impact of reduced intensity regimen or TBI on fertility.

Female allograft patients have been reported to have higher rates of ceaserean section, preterm delivery and low birthweight babies than a control population.[6] However, BMTSS did not find a higher prevalence of preterm births after HCT than in the sibling comparison group, a finding that is similar to that of our study.[7]

It should be stated that there are drawbacks of this study. The study was designed retrospectively which involved missing data of patients'/patient partners' hormone levels. Since, we don't have adequate data about fertility prior to transplantation, it is also possible that partners of the patients but not the patients themselves may be infertile.

Two partners of our patients conceived with assisted reproductive technologies (ARTs) which have been recently evolving such as in vitro fertilization-embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer and frozen embryo transfer. Currently, fertility preservation should be considered prior to cytotoxic treatments. Sperm cryopreservation is an option for male patients. Female patients have more options to consider, including ovarian cortex freezing, oocyte cryopreservation after conventional in vitro fertilization stimulation, in vitro fertilization and embryo freezing, drug-based preservation with gonadotropin releasing hormone (GnRH) agonists and transposition of the ovaries prior to radiotherapy, which are all techniques of fertility preservation.[15]

CONCLUSION

Treatments prior to Allo-HSCT may have damaging effects on gonadal tissue and induce infertility as previously reported. A benign nature of the initial diagnosis, early age at diagnosis and at Allo-HSCT, no relapse of the primary disease, and a bone marrow stem cell source are associated with fertility in our study. Unexpectedly, we found no relationship of infertility to the myeloablative conditioning regimen, radiotherapy/chemotherapy prior to Allo-HSCT, TBI usage and frequency, donor type or development of acute and chronic GVHD.

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