Stem Cell Transplantation

Low prevalence of premature ovarian failure in women given reduced-intensity conditioning regimens for hematopoietic stem-cell transplantation

A survey was done to determine the prevalence of premature ovarian failure among female transplant patients. Within the 109 patients who replied, premature ovarian failure was found to be less common among women given reduced-intensity conditioning regimens (37.5%) than among those given high-dose conditioning regimens (79%) for hematopoietic stem-cell transplantation (p=0.007).

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Patients who survive after hematopoietic stem-cell transplantation (HSCT) can experience decrements in various aspects of quality of life particularly the physical aspect due to the side effects of the conditioning regimens or from the long-term effects of the transplant. Among female survivors, reproductive dysfunction can lead to premature ovarian failure and its consequences can significantly affect these patients' post-transplant quality of life. As more young female patients become long-term survivors after HSCT, attention to treatment-induced premature ovarian failure and subsequent infertility is needed.

The traditional conditioning regimens (high-dose chemotherapy ± total body irradiation) used in HSCT have been fully myeloablative. These regimens are highly intense and quite gonadotoxic, leading to premature ovarian failure in 70% to 100% of women receiving them.[1-7] Chemotherapy regimens used in non-transplantation settings are, in contrast, usually less intense and less gonadotoxic. The incidence of premature ovarian failure was reported to be 40-70% in women who underwent certain chemotherapeutic regimens for breast cancer or Hodgkin's disease.[8-9] Recently developed reduced-intensity conditioning (RIC) regimens in HSCT use less intense chemotherapy ± low dose radiation therapy. These regimens typically evoke less treatment-related toxicity than traditional high-dose conditioning (HDC) regimens, but only a few reports are available regarding the occurrence of premature ovarian failure among patients with aplastic anemia who received cyclophosphamide alone before HSCT.[3] No studies have been conducted on the risk of premature ovarian failure after the use of other RIC regimens prior to HSCT.

We identified 212 female patients (179 treated with HDC and 33 with RIC) in our database who underwent HSCT between January 1987 and September 2001, who were alive at the time of this study, were 16 to 40 years old at the time of the transplant and had no history of breast or ovarian cancer. Questionnaires on menstruation history before and after the transplant and use of any hormonal drugs were sent to 166 patients with contact information (138 in the HDC group and 28 in the RIC group). One hundred and nine patients (89 in the HDC group and 20 in the RIC group) replied. Ovarian failure was defined according to World Health Organization as no menstruation for at least 12 months, in the absence of pregnancy or use of hormones.[10] The characteristics of the patients who replied and those who did not in both the HDC and RIC groups were compared statistically, and no significant differences were found in terms of age or disease status at transplant, number of prior chemotherapy or biological therapy regimens, type of transplant, or conditioning regimen (Table 1). Among the patients who replied, the median age at transplant of the 89 patients in the HDC group was 33 years (range, 17–40 years) and the median follow-up period was 75 months (range, 12–190 months). For the 20 patients in the RIC group, the median age at transplant was 32.5 years (range, 17–40 years) and the median follow-up period was 22 months (range, 17–40 months). No statistically significant differences were found in the characteristics of the patients between these two groups (Table 2). With regard to ovarian function, 16 of the 109 patients (12 [13%] of the 89 HDC patients and 4 [20%] of the 20 RIC patients) reported having not menstruated during the 12 months preceding the transplant and thus were removed from the analysis. Of the remaining 93 patients with functional ovaries before the transplant (77 HDC, 16 RIC), 61 patients (79%) in the HDC group lost ovarian function after the transplant as compared with only 6

Table 1. Patients' characteristics by reply status.

	Replied	*Did not reply*	*p value*
No. of patients	109	57	value
Median age at transplant, years (range)	33 (17–40)	31 (18–40)	0.09
Disease status, No. of patients (%)			
Early*	36 (33%)	12 (21%)	0.08
Advanced°	73 (67%)	45 (79%)	
Median no. of prior Chemotherapy cycles (range)	2 (1–4)	2 (0–6)	0.8
Median no. of prior biological therapies# (range)	0 (0–1)	0 (0–4)	0.3
Type of transplant, no. of patients (%)			
Allogeneic	68 (62%)	30 (53%)	0.2
Autologous	41 (38%)	26 (46%)	
Conditioning regimen, no. of patients (%)			
High dose	89 (82%)	49 (86%)	0.5
Reduced intensity	20 (18%)	8 (14%)	

**Early disease status: any untreated disease, any disease in first complete or partial response, or chronic myelogenous leukemia in first chronic phase; °advanced disease status: any disease status not included in the definition of early disease status; #excluding hormonal therapies.*

Table 2. Patients' characteristics by conditioning regimen.

	Conditioning Regimen		
	High dose	*Reduced intensity*	*p value*
No. of patients	89	20	
Median age at transplant years (range)	33 (17-40)	32.5 (17-40)	0.4
Disease status, no. of patients (%)			
Early*	28 (31%)	8 (40%)	0.4
Advanced°	61 (69%)	12 (60%)	
Median no. of prior chemotherapy cycles (range)	2 (0-3)	2 (1-4)	0.5
Median No. of prior biological therapies# (range)	0 (0-2)	0 (0-4)	0.4
Type of transplant, no. of patients (%)			
Allogeneic	55 (62%)	13 (65%)	0.8
Autologous	34 (38%)	7 (35%)	
Ovarian function before transplant, no. of patients (%)			
No	12 (13%)	4 (20%)	0.5
Yes	77 (87%)	16 (80%)	
Ovarian function after transplant, no. of Patients (%)			
No	61 (79%)	6 (37.5%)	
Yes	16 (21%)	10 (62.5%)	0.007

**Early disease status: any untreated disease, any disease in first complete or partial response, or chronic myelogenous leukemia in first chronic phase; °advanced disease status: Any disease status not included in the definition of early disease status; #excluding hormonal therapies.*

patients (37.5%) in the RIC group (p=0.007).

Our results show that premature ovarian failure was less prevalent when patients were given RIC rather than HDC regimens in preparation for HSCT. The prevalence of premature ovarian failure among patients given RIC regimens for HSCT in our study (37.5%) was similar to the 40% to 70% rate among patients given chemotherapy for purposes other than transplantation. Since our study was retrospective in nature, we relied on returned questionnaires for information. Only the prevalence but not the incidence of premature ovarian failure in our population was ascertained. However we compared the characteristics of patients who replied and those who did not and found no significant differences. Therefore those who replied could be a representative sample for the whole patient population. Given the rapid increase in the use of HSCT, many more patients will become eligible for this kind of treatment. Curing the disease is no longer the only goal; ensuring a better quality of life after the transplant is as important. We propose a prospective study to determine the exact role of RIC regimens on the overall incidence of premature ovarian failure.

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