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ORIGINAL ARTICLE

Quality of life, reproduction and sexuality after stem cell transplantation with partially T-cell-depleted grafts and after conditioning with a regimen including total body irradiation

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Thirty-four men and 36 women (median age 43 and 45 years, respectively) underwent stem cell transplantation (SCT) for acute leukaemia in first complete remission or chronic myelogenous leukaemia in first chronic phase between 1981 and 2001 from HLA-identical siblings. The conditioning regimen included TBI and all grafts were partially depleted of T cells. Changes in quality of life (QOL), reproduction and sexuality were studied using a questionnaire, and the previously given information related to these problems was assessed. In addition, endocrine status was assessed and semen analysis was performed. After SCT, patients reported less energy ($n = 50$) and a deterioration in the job situation ($n = 31$). Patients experienced a negative change in sexual relations ($n = 41$). Important problems of sexual dysfunction were vaginal dryness in women ($n = 19$) and erectile dysfunction in men ($n = 16$). None of the patients was fertile based on their gonadotrophin levels, sperm concentrations and reproductive outcomes. Women experienced climacteric symptoms ($n = 24$). Quality of life was negatively influenced by these changes. One-fifth of the patients were not satisfied with the information given with regard to reproduction, premature menopause and sexual problems.

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Introduction

The use of allogeneic stem cell transplantation (SCT) has given rise to a large group of patients with prolonged disease-free survival.[1] As a consequence, long-term effects and quality of life (QOL) become increasingly important in the follow-up of these patients. In spite of the positive prospects, leukaemia, SCT, the conditioning regimen and the unremitting uncertainty about outcome are a substantial emotional burden.[2] Management of iatrogenic gonadal reproductive failure and sexual morbidity are important in young recipients of SCT.[3]

The Nijmegen allogeneic transplantation programme was started in May 1981. This study provides an overview of the problems our patients experienced after SCT with respect to QOL, reproduction and sexuality.

Materials and methods

Patients

The study included patients aged 18–60 years who underwent SCT from an HLA-identical sibling donor between 1981 and 2001 at the Radboud University Nijmegen Medical Centre. The inclusion criteria of this study were transplantation for acute myeloid leukaemia or acute lymphoblastic leukaemia in first complete remission or for chronic myeloid leukaemia in first chronic phase and a conditioning regimen including total body irradiation (TBI).

Patients who were incapable of making decisions, terminal patients, patients with an additional serious disease, patients with another indication for allogeneic SCT and patients who were not conditioned with the addition of TBI were not eligible for this study.

One hundred and seventeen patients, 64 men (55%) and 53 women (45%), were eligible to participate in this study. Patients were approached by mail or during a routine check-up at the outpatient's clinic. Seventy patients (60%) agreed to enter the study and 34 men (49%) and 36 women (51%) completed a questionnaire.

Methods

The questionnaire used was based on the one used for the EORTC-GIMEMA AML 8A trial, which was derived from the EORTC-QLQ c30.[4,5] The questionnaire contained questions relating to the patient's condition in the previous week and patients were asked to answer questions concerning changes after SCT. The study was performed

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at a median of 81 months (range: 18–198 months) and 76 months (range: 17–219 months) after SCT for men and women, respectively. Questions were asked on demographic data, state of health, reproduction and sexuality.

With regard to QOL, global health status was assessed in seven questions on a scale with dichotomous response categories (yes or no). In addition, global assessment of overall physical condition, overall QOL, relationship with partner and professional life was made by a 5-point Likert scale ranging from bad to good. The questionnaire also included a disease-related modifications module; patients were asked to evaluate the changes induced by their disease and treatment in several domains with a 5-point scale of changes, ranging from far worse to far better.[4]

Questions that involved reproduction, menstrual cycle, climacteric symptoms and use of oral contraceptives and hormone replacement therapy (HRT) were added.

Sexual dysfunctions categorized according to the Diagnostic and Statistical Manual of Mental Disorder (DSM IV) were divided into disorders of desire, arousal, orgasm and pain. Study-specific single-item questions included interest in sex, sexual activity, pleasure from sex, pain during sexual intercourse and delayed or absence of orgasm.[4] Questions on vaginismus and vaginal dryness for women and erection problems and early ejaculation for men were added. These items were assessed on a 5-point scale.

Finally, questions were created as an inventory of the information given on all the problems mentioned above.

Apart from the questionnaire, endocrine status was assessed. As most women used HRT or combined oral contraceptives, hormone levels were measured after a hormone-free interval of at least 1 month. The following basal hormone levels were tested: luteinizing hormone (LH), follicle-stimulating hormone (FSH), oestradiol, progesterone and testosterone. Blood sampling in male patients was carried out at any opportune occasion. Luteinizing hormone, FSH and testosterone were tested. Furthermore, semen analysis was performed according to the WHO standards.

SPSS was used for statistical analysis. Non-parametric tests and χ^2 test were used to compare data. *P*-values <0.05 were considered statistically significant.

Results

Forty-seven of 117 patients (40%) did not participate; 64% were men. Only eight explained their refusal: no interest or SCT many years ago. There was no significant difference between the ages of the non-responders and the responders. Eight of the patients who did not participate were immigrants and linguistic difficulty may have contributed to their refusal.

Patient characteristics

Table 1 shows patient characteristics. Before the diagnosis of leukaemia, 47 patients (67%) were married or lived together based on mutual agreement. At the time of the questionnaire, 54 patients (77%) had an official relationship with a partner.

The highest obtained school level of the male participants was higher than that of the women. Twenty-seven men (79%) took education after their eighteenth year (specialized education, bachelor or master degree) and the number of women was 20 (56%). After the transplantation, job situations had changed for many patients; 20% had been declared unfit to work, 13% worked less hours and 16% had started working after completing school. The median interval between termination of the intensive treatment and resumption of work was 8 months (range: 3–33 months) and 7 months (range: 3–39 months) for men and women, respectively ($P > 0.05$).

Quality of life

After SCT, the estimation of overall QOL declined in 44% of patients. After the diagnosis of leukaemia, two-thirds of the patients reported less energy. Thirty-four per cent of the patients experienced a poorer intellectual capacity. Twenty-nine patients (41%) were limited in doing their work or household jobs and the ability to cope with working conditions had declined for 44%. Meanwhile, 53% of the patients rated their mood as being unchanged. Sexual relations had deteriorated in 59%. More than a quarter of the patients perceived their social relationships as worsened, but family life had improved in 33%.

Other items are shown in Tables 2 and 3.

Endocrine status in male patients

This was evaluable in 26 men (77%). Follicle-stimulating hormone levels were raised in all men. Luteinizing hormone levels were normal in 20 men and raised in six men.

Table 1 Patient characteristics

	Men	*Women*
Number of patients	34	36
Age (years), median (range)	43 (24–59)	45 (23–59)
<50 years, *n* (%)	22 (65)	21 (58)
Age at SCT (years), median (range)	32 (16–54)	36 (14–54)
Diagnosis, n (%)		
AML	8 (24)	16 (44)
ALL	9 (26)	4 (11)
CML	17 (50)	16 (44)

Abbreviations: ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; CML = chronic myeloid leukaemia; SCT = stem cell transplantation.

Table 2 Global health status after SCT

	Men n *(%)*	*Women* n *(%)*	P-*value*
Trouble in some kind of strains	11 (32)	17 (47)	0.204
Trouble in taking a long walk	9 (27)	13 (36)	0.431
Trouble in taking a short walk	1 (3)	0 (0)	0.300
Most of the day in a bed or chair	0 (0)	0 (0)	1.000
Needing help for activities of daily living	0 (0)	0 (0)	1.000
Limited in doing work/household jobs	14 (41)	15 (42)	0.967
Not able to do work/household jobs	0 (0)	3 (8)	0.157

χ^2 test of difference between men and women; *P*-values <0.05 are considered statistically significant.

Table 3 Disease-related changes after SCT

	Men n *(%)*			*Women* n *(%)*			P-*value*
	Diminished	*No change*	*Improved*	*Diminished*	*No change*	*Improved*	
Energy	26 (76)	5 (15)	3 (9)	24 (67)	9 (25)	3 (8)	0.558
Mood	11 (32)	19 (56)	4 (12)	10 (28)	18 (50)	8 (22)	0.509
Intellectual capacity	13 (38)	19 (56)	2 (6)	16 (44)	15 (42)	4 (11)	0.488
Family life	3 (9)	17 (50)	12 (35)	4 (11)	20 (56)	11 (30)	0.862
Sexual relationship	19 (56)	13 (38)	2 (6)	22 (61)	9 (25)	3 (8)	0.564
Professional life	15 (44)	12 (35)	5 (15)	16 (44)	15 (42)	3 (8)	0.668
Social relationship	11 (33)	13 (38)	10 (29)	9 (25)	19 (53)	8 (22)	0.474
Leisure activities	12 (35)	13 (38)	9 (27)	10 (28)	14 (39)	12 (33)	0.744
Overall quality of living	13 (38)	12 (35)	9 (27)	11 (30)	14 (39)	10 (28)	0.836

χ^2 test of difference between men and women; *P*-values <0.05 are considered statistically significant. *Note*: not all patients answered all questions.

Testosterone was low normal in 21 men (81%); the remaining men (19%) had reduced testosterone levels. Figure 1 shows FSH, LH and testosterone levels in a scattergram.

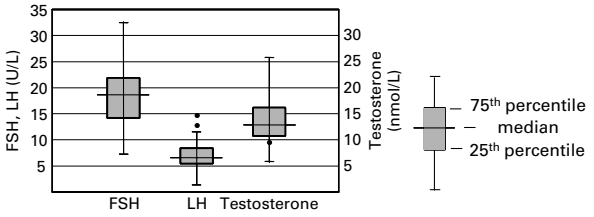

Figure 1 Hormone assays – men (reference intervals: follicle-stimulating hormone 2–7.5 U/l, luteinizing hormone 1.5–9.2 U/l, testosterone 11–45 nmol/l).

Endocrine status in female patients and climacteric symptoms

This was evaluable in 27 women (75%). Postmenopausal FSH levels (>40 U/l) were seen in 20 women (74%). Six women (22%) had FSH levels between 20 and 40 U/l, which signifies ovarian insufficiency. Additionally, the LH levels were raised in accordance with these FSH levels. Oestradiol levels were <150 pmol/l in 25 women. Follicle-stimulating hormone, LH and oestradiol levels are illustrated in Figure 2a. Progesterone was below the detection limit (<1.3 nmol/l) in all women. Testosterone ($n=22$) was low normal in 16 women and six women had a testosterone below the detection limit (0.52 nmol/l) (Figure 2b).

Before the diagnosis of leukaemia, four women (11%) had climacteric symptoms of whom two women (6%) already had reported amenorrhoea before the onset of the disease. All of these women were older than 40 years. After SCT, none of the women had resumed a spontaneous menstrual cycle anymore; 56% of these women were younger than 40 years. Twenty-four women (67%) had reported hot flushes and night sweats, as well as vaginal dryness, mood swings and bone pain after SCT. Thirteen women (36%) used oral contraceptives and 10 women (28%) used HRT.

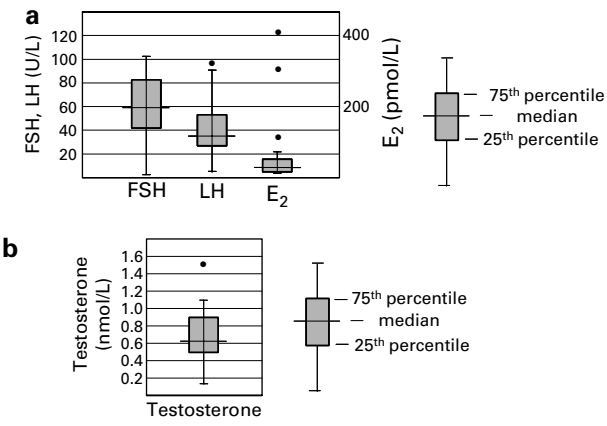

Figure 2 (**a**) Hormone assays – women (follicle-stimulating hormone (FSH) levels >40 U/l = postmenopausal status, FSH levels 20–40 U/l = ovarian insufficiency, luteinizing hormone levels >12 U/l in combination with raised FSH levels = postmenopausal status, E_2 levels <150 pmol/l = oestrogen deprivation). (**b**) Testosterone – women (reference interval: 0.52–2.40 nmol/l).

Sexuality

At the time of the study, 85% of the men and 81% of the women had an active sexual relationship. Interest in sex, sexual activity and pleasure from sex deteriorated in almost 60% of the patients; half of these patients were aged <50 years (Table 4). After cessation of the intensive treatment, the interval of resumption of sexual activity varied from 1 to 104 weeks for both men and women with a median of 16 and 12 weeks for men and women, respectively ($P>0.05$).

Forty-seven per cent of the men had experienced erectile dysfunction more often than before SCT. Forty-four per cent of these men were aged <50 years. A quarter of the men stated to have erectile dysfunction always or often during the last week. Furthermore, 38% of the men had a delay or absence of orgasm/ejaculation more frequently than before SCT; 62% of these men were aged <50 years.

The most important complaint of women was vaginal dryness, which was experienced more often after SCT by 53% of the women. Forty-seven per cent of these women were aged <50 years. One-third of the women had experienced this problem always or often during the last week. The frequency of other problems, such as pain during sexual intercourse and early orgasm or ejaculation in men and pain during sexual intercourse, vaginismus and delayed or absence of orgasm in women, is shown in Table 5.

Table 4 Sexual function after SCT

	Men n *(%)*			*Women* n *(%)*			P-*value*
	Diminished	*No change*	*Improved*	*Diminished*	*No change*	*Improved*	
Interest in sex	19 (56)	13 (38)	2 (6)	22 (61)	10 (28)	2 (6)	0.737
Sexual activity	21 (62)	8 (24)	5 (15)	20 (56)	10 (28)	2 (6)	0.479
Pleasure from sex	20 (59)	10 (29)	4 (12)	19 (53)	8 (22)	3 (8)	0.932

Abbreviation: SCT = stem cell transplantation.
χ^2 test of difference between men and women; *P*-values <0.05 are considered statistically significant. *Note*: not all patients answered all questions.

Table 5 Sexual dysfunction after SCT

	Increased n *(%)*	*No change* n *(%)*	*Decreased* n *(%)*
Men			
Pain during sexual intercourse	4 (12)	26 (77)	1 (3)
Erectile dysfunction	16 (47)	17 (50)	0 (0)
Delayed or no orgasm/ejaculation	13 (38)	18 (53)	2 (6)
Early orgasm/ejaculation	6 (18)	18 (53)	9 (27)
Women			
Pain during sexual intercourse	7 (19)	16 (44)	3 (8)
Vaginismus	2 (6)	21 (58)	3 (8)
Vaginal dryness	19 (53)	8 (22)	0 (0)
Delayed or no orgasm	7 (19)	14 (39)	5 (14)

Note: not all patients answered all questions.
Abbreviation: SCT = stem cell transplantation.

Reproduction
After the transplantation, none of the men had offspring by means of spontaneous conception or cryopreserved semen. Twenty-two of these men (65%) were aged <50 years. After transplantation, 10 women (28%) wanted to become pregnant. These women were all aged <40 years at SCT. Out of these, only one woman had become pregnant after 9 months through oocyte donation with *in vitro* fertilization (IVF) and one woman had adopted two children.

Semen analysis
The number of men who produced semen for analysis was 15 (44%). In 19 men (56%), no semen analysis was performed. Of these, four (21%) had explicitly refused. Five men (26%) had been sterilized before the onset of the disease and 10 men (53%) did not give a particular reason for refusing.

All men had sperm concentrations below the pathological range of 10×10^6/ml according to the WHO standards. Azoospermia was shown in 13 men (87%). The other two men (13%) had severe oligospermia with sperm concentrations of $<0.1 \times 10^6$/ml. The sperm volume in 11 men (73%) was normal according to the WHO standards, whereas four men (27%) produced a volume below the normal range (<2.0 ml).

Counselling
Additional questions related to the information on the consequences of the disease given to the patients before and during the treatment. Three women (8%) were not acquainted with the possibility of premature menopause as a result of the conditioning regimen and four women (11%) were not informed on consequent infertility. Six men (18%) were not aware of the possibility of cryopreservation of semen. Twenty-one patients (30%) reported to have received little or no information on the consequences with regard to sexuality.

As a result, almost 20% of the patients were dissatisfied with the received information with regard to infertility and premature menopause; sexual problems were not discussed in particular.

Discussion

The response rate of 60% (70 out of 117 patients) was considered reasonable as questionnaires were sent by mail and the overall impression of the response appeared to be representative.

As patients were also asked to answer questions concerning changes after SCT, the influence of SCT could be examined.

Chiodi *et al*.[6] suggested that recovery of QOL may be considered complete in the great majority of patients (70%) after 1–2 years, but additional improvements may occur later. It was also suggested that recovery might be delayed in older patients. Andrykowski *et al*.[7] concluded that the disease diagnosis, dose of TBI, presence of chronic GVHD, type of GVHD prophylaxis and extent of marrow graft match were not associated with QOL after SCT. These and other topics could be investigated in subsequent cohort studies.

The present study shows that two-thirds of the patients had less energy after SCT. A large proportion of BMT survivors are impaired by fatigue as long as 10 years following treatment.[2] However, Syrjala *et al*.[8] showed that physical function was most impaired at 90 days post transplant, with a return to pre-transplant levels of functioning after 1 year. They also showed that 68% of 67 allogeneic transplant patients had returned to full-time work by 2 years post transplant. This percentage corresponds with the results in our study, although job situations had declined for 44% of our patients. Andrykowski *et al*.[7] reported a percentage of 33% of 119 patients of whom medical problems had resulted in unemployment or early retirement. Loss of employment was associated with lower social functioning, chronic GVHD and job discrimination for the women in particular.[9]

The influence of SCT on sexual dysfunction has been confirmed by several studies.[6,7,10] Little is known, however, about sexual functioning before SCT. In the present study, patients experienced more sexual problems after transplantation in comparison to the period before SCT. Although some of these negative outcomes will be caused by SCT, we cannot determine which changes occur as a function of general changes in physical condition. Zittoun *et al*.[4] reported decreased interest in sex, sexual activity and pleasure from sex in 30–41% of 98 patients. Our study shows higher percentages varying from 56 to 59%. Several reasons for these differences might be given, among other differences in study population. Watson *et al*.[10] reported on the negative correlation between age and sexual satisfaction after SCT. Furthermore, Chiodi *et al*.[6] concluded that women showed significant greater decrement in sexual relations compared to men. Earlier analysis has shown that TBI, long-term sequelae, chronic GVHD and sterility are associated with sexual dysfunction in women, but not in men. Lack of vaginal lubrication appears to be the most important cause.[11] Hormone replacement therapy is then a viable option for the sexual problems of women following SCT. Neizert *et al*.[2] mentioned the absence of research with positive outcome of this treatment for male patients after SCT. Changes in erectile dysfunction in response to treatment can be detected by the International Index of Erectile Function (IIEF).[12]

After transplantation, incapability of reproduction is shown in all patients, as indicated by their gonadotrophin levels, sperm concentrations and reproductive outcomes. These results are in accordance with other studies.[13–16] Mertens *et al*.[13] showed evidence of gonadal dysfunction in 92% of the male patients and 99% of the female patients. Raised FSH levels in men represent damage to the Sertoli cells, which assist spermatogenesis, and normal LH and testosterone levels are due to the maintenance of Leydig cell function. In women, FSH and LH levels rise and oestradiol levels fall owing to follicular destruction as a result of chemotherapy and radiotherapy.[17] In the study of Mertens *et al*.,[13] older age at SCT was correlated with an increased risk in the development of elevated gonadotrophin levels. They concluded that women were not only more likely to develop elevated gonadotrophin levels than men, but also did so earlier after SCT. Furthermore, they demonstrated that individuals who received radiation were more likely to develop an elevated FSH level over time than those who did not. In addition, they reported data that support the theory that fractionated TBI is more deleterious to spermatogenesis than single fraction TBI or total lymphoid irradiation (cumulative probabilities of developing elevated FSH levels were 96.6, 76.6 and 71.9%).

In the present study, none of the patients had offspring by means of spontaneous conception. Men who undergo SCT should be offered cryopreservation of semen as soon as possible after the diagnosis and before any treatment.[18,19] Female fertility potential can be safeguarded by IVF with cryopreservation of embryos. Cryopreservation of ovarian tissue is still in an experimental stage and carries the risk of reimplantation of the cancer. Methods to counter gonadotoxic effects are studied. Chatterjee *et al*.[3] have stated the necessity of prospective data and randomized controlled studies to determine the clinical potential of GnRH agonist co-treatment in the prevention of chemo-radiotherapeutic damage. Sometimes, spontaneous restoration of fertility occurs. A few case reports have been published on pregnancies after allogeneic SCT with a conditioning regime including TBI. Male patients were more likely to experience gonadal recovery than female patients.[13] The study of Jacob *et al*.[20] identified six patients out of 46 who recovered fertility or spermatogenesis. Restoration of spermatogenesis has even been demonstrated after 9–10 years.[18] The potential harm of chemotherapy and/or TBI to offspring has not been demonstrated as yet. Next to normal-term deliveries with healthy offspring, an increased incidence of pre-, peri- and postpartum complications has been reported. Also, an increased risk of spontaneous abortion, preterm delivery, low birth weight and caesarean section has been described.[21,22] Because of the possible restoration of fertility after SCT, patients should be counselled with regard to contraception.

As loss of gonadal function has a major impact on QOL, we agree with Chatterjee *et al*.[19] that reproductive specialists should be part of the transplant team in patients of child-bearing years and that reproductive management should begin before transplantation. Adequate counselling should inform patients on the potential risks of the proposed therapy with regard to gonadal function and the reproductive tract. It should invite discussion on the options available for preserving fertility and reducing psychosexual morbidity. This should give the patients a better chance to anticipate on the expected problems and to influence QOL in a favourable way. In future, many of the problems encountered may be prevented by less intensive conditioning regimens.

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