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Sexual Health in Hematopoietic Stem Cell Transplant Recipients

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Abstract

Hematopoietic stem cell transplantation (HSCT) plays a central role in patients with malignant and, increasingly, nonmalignant conditions. As the number of transplants increases and the survival rate improves, long-term complications are important to recognize and treat to maintain quality of life. Sexual dysfunction is a commonly described but relatively often underestimated complication after HSCT. Conditioning regimens, generalized or genital graft-versus-host disease, medications, and cardiovascular complications as well as psychosocial problems are known to contribute significantly to physical and psychological sexual dysfunction. Moreover, it is often a difficult topic for patients, their significant others, and health care providers to discuss. Early recognition and management of sexual dysfunction after HSCT can lead to improved quality of life and outcomes for patients and their partners. This review focuses on the risk factors for and treatment of sexual dysfunction after transplantation and provides guidance concerning how to approach and manage a patient with sexual dysfunction after HSCT.

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CONFLICT OF INTEREST DISCLOSURES

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Keywords

late effects; sexual health; survivorship; toxicity; transplantation

INTRODUCTION

As hematopoietic stem cell transplantation (HSCT) becomes more common and survivorship after transplantation increases, it is important to evaluate the impact of long-term complications on quality of life (QOL).[1–6] One common yet seldom discussed effect of both allogeneic and autologous HSCT is sexual dysfunction.[7,8] A longitudinal study performed in 2007 by Humphreys et al among HSCT recipients demonstrated that close to one-half of participants did not have a discussion with their physicians regarding sexual concerns.[9] Similarly, in another study, greater than one-half of women were interested in discussing the impact of treatment on sexual health, but 82% of HSCT recipients reported no such discussion with their providers.[10] Although many patients do attempt to address the issue of their sexuality, physicians often feel unqualified in this field, mainly because they view themselves to be insufficiently prepared to support their patients. To our knowledge, to date specialized teams in sexuality are not available in the majority of long-term transplantation clinics.

Sexual dysfunction is the difficulty experienced by an individual or a couple during any stage of sexual activity, including physical pleasure, desire, preferences, arousal, or orgasm. Sexual dysfunction after HSCT can arise from many causes and is often complex and multifactorial. Studies have shown that graft-versus-host disease (GVHD) and conditioning regimens, including chemotherapies and total body irradiation (TBI), may play a direct or indirect role in sexual health after transplantation.[7,11,12] Documented complications affecting sexuality include decreased libido, genital GVHD, hormonal dysfunction, erectile dysfunction (ED), dyspareunia, and infertility.[11–13] In addition to physical health conditions, psychosocial problems also may contribute to sexual dysfunction in survivors of HSCT.

It is important for health care providers to recognize sexual dysfunction and its effect on QOL as a complication of HSCT. This review examines the available longitudinal studies, prospective studies, and systematic reviews regarding sexual dysfunction after HSCT. Moreover, guidance for health care providers concerning how to manage sexual health problems in long-term survivors of HSCT is proposed.

MATERIALS AND METHODS

References were identified through an electronic search of Medical Literature Analysis and Retrieval System Online (MEDLINE) and Web of Science. We used broad keyword searches for sexual dysfunction after HSCT, genital GVHD, and side effects of conditioning regimens. The following search terms were used: hematopoietic stem cell transplantation, bone marrow transplantation, sexual dysfunction, quality of life, and long-term complications. To identify additional relevant articles, a search of references related to eligible studies also was included. Studies were eligible for inclusion if they assessed the

QOL or psychosocial impact of HSCT on patients and/or caretakers, analyzed conditioning regimens for sexual dysfunction, or analyzed genital GVHD.

Sexual Dysfunction in General Female and Male Populations

A clinical diagnosis of sexual dysfunction requires a sexual issue associated with personal distress that is not assessed in most studies.[14] Although sexual dysfunction rarely threatens physical health, it can take a heavy psychological toll, bringing on depression, anxiety, and debilitating feelings of inadequacy.[15,16] Depression and anxiety or their treatments may also impair sexual function. The types of sexual dysfunction experienced by women include a lack of sexual desire, difficulty achieving orgasm, anxiety or pain during intercourse, or inadequate lubrication. Sexual dysfunction also is common in men and increases with age. Male sexual dysfunction includes decreased libido, ED, and ejaculatory disorders.[17]

Sexual Dysfunction in Female and Male Survivors of HSCT

Multiple studies have indicated that men and women are less likely to be sexually active after HSCT and that nearly one-half of patients experience impaired sexual function after HSCT.[9,13,18–20] Men and women experience a reduction in the quality and quantity of sexual activity, which often leads to anxiety, depression, decreased self-esteem, and stress.[21] Both sexes experience body image issues that lead to decreased sexual desire or the perception that they are less desirable.[22] However, several prospective studies have shown that men were generally able to return to baseline sexual function after 2 to 3 years whereas women were less likely to return to baseline even after long-term follow-up.[11–13] Infertility is also more common among survivors of HSCT compared with controls.[23] In addition, a survey examining the QOL of spouses and partners demonstrated that they experienced more sexual dysfunction than controls, indicating that the effect of HSCT on partners also plays a significant role in sexual health after HSCT.[24,25] In a survey of women with cancer who were undergoing treatment, including HSCT recipients, 77% reported severe problems with at least 1 sexual health domain (libido, vaginal dryness, dyspareunia, and patient and partner satisfaction) at the 1-year follow-up.[10]

Risk factors for sexual dysfunction after HSCT include conditioning regimens, systemic or genital GVHD, medications, cardiovascular complications, psychosocial distress, and other reasons (drug interaction, infertility, and general health burden) (Table 1). These risk factors can be either directly involved in sexual dysfunction (eg, in the case of genital GVHD manifestations) or indirectly involved (eg, in patients with premature cardiovascular complications).

Conditioning Regimen

The side effects of conditioning regimens, especially alkylating agents and TBI, contribute to sexual dysfunction. Common acute side effects of chemotherapy and TBI, (Table 1) including nausea, vomiting, hair loss, and fatigue, can induce loss of interest and desire for sexual activity. Moreover, alkylating agents (eg, cyclophosphamide) and TBI have been shown to be directly toxic to gonadal function.[26] TBI has been reported to play a central role in male and female infertility in several studies, with a more profound effect noted in men.[12,27,28] Long-term effects on the hypothalamic-pituitary-gonadal axis from conditioning

regimens can cause vaginal dryness, dyspareunia, and premature ovarian insufficiency in women. The incidence of premature ovarian failure after HSCT ranges from 40% to 100%.[27,28] Men are likely to experience a decrease in sexual drive, azoospermia, and ED.[11,13,29–31]

Several studies have indicated that germ cell damage and Leydig cell insufficiency occur after high-dose chemotherapy and TBI.[27,32–35] In addition, there are cases of high-dose chemoradiation causing acute functional castration within 72 hours of TBI and 50% loss of testicular volume.[26,36] A study by Anserini et al demonstrated that 70.3% of men had azoospermia, with faster recovery observed in patients undergoing chemotherapy-only conditioning regimens (1–3 years for recovery) versus patients undergoing chemoradiation (4–9 years for recovery).[31] The results of another study indicated that cavernosal arterial insufficiency from chemoradiation contributed to ED in patients with hematological malignancies.[32] Although we did not find published data specifically regarding the effect of high-dose cyclophosphamide (which constitutes the most common myeloablative regimen either with TBI or with busulfan) on the risk of sexual dysfunction in patients with HSCT, ample data from cancer and rheumatology studies have indicated a substantial risk of male infertility[37] as well as amenorrhea and infertility in females from the use of cyclophosphamide.[38,39]

Genital GVHD

A commonly described long-term complication after HSCT is chronic GVHD. Chronic GVHD can affect multiple organ systems, with manifestations in the skin, lung, liver, gastrointestinal tract, and mucous membranes, leading to poorer QOL. Several studies have shown that patients have lowered emotional well-being and decreased sexual satisfaction, arousal, and orgasm after developing chronic GVHD.[13]

Moreover, chronic GVHD can cause genital manifestations in female and male long-term survivors of HSCT and be directly involved in sexual dysfunction (Table 1). In women, gynecological GVHD manifestations affect between 29% to 49% of women and include vaginal dryness, dyspareunia, amenorrhea, vulvar or vaginal scarring, vaginal stenosis, and loss of libido.[11,40] The onset is usually between 6 and 12 months after HSCT, but may arise later.[12] These complications overlap with premature ovarian failure from conditioning regimens.

Genital GVHD was previously described only rarely in men, but to our knowledge the 2014 National Institutes of Health Consensus Development Project on chronic GVHD criteria has for the first time included male genital GVHD as a complication.[41] The project describes the diagnostic features of GVHD as lichen planus-like or lichen sclerosis-like features, phimosis, urethral scarring, and stenosis. To the best of our knowledge, before 2013, only 8 cases in men were described and involved inflammation of genitalia, adhesions, decreased libido, and ED.[7,12] Mueller et al performed a prospective cross-sectional study that examined 155 men before and after HSCT in 2013. Of the 155 patients, 31 patients had posttransplantation genital skin changes that were divided into inflammatory and noninflammatory changes. Inflammatory changes included balanoposthitis, lichen sclerosis, and phimosis and were found to be closely associated with other GVHD manifestations.

Moreover, ED was significantly more frequent in patients with inflammatory genital changes.[12]

Cardiovascular Disease

In the general population, male patients with risk factors for cardiovascular disease and evidence of cardiovascular disease have an increased risk of ED (Table 1).[42] Long-term survivors of allogeneic and autologous HSCT are at risk of premature cardiac and cardiovascular late effects.[43] However, only 2.4% of patients after autologous HSCT[44] and 3% after allogeneic HSCT have been reported to have mortality directly related to cardiac toxicity.[45] In addition, to the best of our knowledge, there are no data regarding ED in patients with cardiac complications after HSCT, which may underestimate the true incidence of ED in the HSCT population.

Psychosocial Distress

Depression and medications to treat depression, fatigue, and stress are recognized as risk factors associated with decreased libido in the general population (Table 1). The prevalence of psychiatric diagnoses in survivors of HSCT has been reported to be as high as more than double that of the general population and in one study, 5% of survivors met the diagnostic criteria for posttraumatic stress disorder.[46] Transplant recipients commonly report concerns about disease recurrence and an inability to return to their pretransplant level of functioning. Survivors of allogeneic HSCT report problems with psychological adjustment and memory disturbances and 15% to 25% of survivors reported significant emotional distress, low self-esteem, and suboptimal satisfaction with life. However, to our knowledge, there are no studies regarding the impact of psychosocial distress on sexual dysfunction in long-term survivors of HSCT.

There are data to suggest that early intervention in the form of a discussion regarding the side effects of HSCT improved sexual function in patients[9] (Table 1). Fatigue, depression, and body changes are common complications and should be discussed as part of the HSCT evaluation. A recent Danish study that used semistructured in-depth interviews from survivors of HSCT indicated that bodily changes and symptoms related to chronic GVHD led to physical limitations or altered body image, which directly and indirectly resulted in sexual dysfunction or problems with intimacy.[22] High-dose corticosteroids are part of the treatment of GVHD and are known to suppress endogenous hypothalamic and adrenal hormones. This treatment can have a profound physical and emotional impact on patients. Cushingoid features with weight gain and loss of muscle mass as well as joint problems can lead to feelings of unattractiveness and decreased sexual desire. Thus, setting expectations with patients and partners, including a frank discussion regarding potential sexual and psychological symptoms from HSCT and conditioning regimens, is important.[26]

Other Causes

Although infertility does not directly relate to sexuality, it can have a profound effect on sexual well-being. If an HSCT recipient desires to have a child, infertility can be a source of distress and anxiety, potentially affecting intimacy, relationships, and sexual health (Table

1). In addition, many patients will be receiving multiple medications after HSCT, which may contribute substantially to sexual dysfunction (Table 1).

The cumulative incidence, morbidity, and mortality of any chronic health conditions increases with time after HSCT.[47] The cumulative incidence of chronic health conditions among survivors at ≥ 10 years after HSCT was found to be significantly higher among those with chronic GVHD compared with those without chronic GVHD, thereby demonstrating the impact of GVHD on general health after HSCT.[48] Furthermore, loss of interest in one's sex life has been widely described in association with illness and fatigue (Table 1).

Guidance for the Screening and Management of Sexual Dysfunction

Screening for sexual dysfunction—With respect to issues regarding sexuality, appropriate surveillance of long-term survivors of HSCT includes asking directly about genital skin symptoms and examining patients for genital changes. In females, this is generally performed as part of the yearly gynecological examination. In males, the genital examination is usually completed by the dermatologist after referral from primary care or hematology. In addition, the assessment of gonadal function is undertaken 1 year after HSCT for all women and includes follicle-stimulating hormone (FSH), luteinizing hormone, and estradiol levels. Subsequent testing is based on symptoms. Among males, gonadal assessment also includes follicle-stimulating hormone and luteinizing hormone as well as testosterone.[5,6,49]

Sexual function is included as part of the routine assessment at 6 months, 1 year, and then annually after HSCT.[1,2] The use of self-reported, standardized questionnaires can enhance patient-provider communication regarding sexual dysfunction by eliciting a patient's symptoms and concerns. Questionnaires can uncover aspects of a patient's sexual issues that otherwise would have gone unspoken. These specific details regarding a patient's circumstances open the door for direct and open discussion concerning sexuality between the patient and the health care provider. Once sexual dysfunction is diagnosed or suspected, the patient can be referred to a specialist, such as a gynecologist, urologist, sexual therapy specialist, or endocrinologist, for further management.

General management of sexual dysfunction—Addressing psychosocial stresses is important for improving a patient's sexual life after HSCT (Table 1). Sex therapy then can be used to treat the psychosocial stressors contributing to sexual dysfunction. Through therapy, concerns regarding sexual function, intimacy, communication between sexual partners, and behavioral strategies can be addressed. If sexual dysfunction is suspected, this option of sex or psychological therapy can be presented candidly with patients.

Melanocortins are a promising drug class for the treatment of ED in men and lack of arousal in women (Table 1). Bremelanotide has been shown to be effective in treating ED in healthy men and increasing arousal in healthy women.[26,50] Because sildenafil cannot be used in conjunction with nitrates, melanocortins may be a safer option in survivors of HSCT. However, to the best of our knowledge, there are no studies published to date regarding the use of bremelanotide in patients after HSCT.

Management of specific changes

Genital changes in women: Genital changes in women are often a consequence of both conditioning regimens and chronic GVHD. In 2 retrospective studies, local and systemic hormonal therapies were used to prevent concomitant estrogen deficiency in women with premature ovarian failure.[11,40] Topical steroids were added for persistent genital lesions despite hormonal therapy.[11] In the study by Zantomio et al, topical cyclosporine for the genital tract was initiated if response to a topical steroid was inadequate. Vaginal self-examination or dilator insertion at least twice weekly was recommended to maintain vaginal capacity to prevent genital tract adhesions and vaginal stenosis.[40] However, a review by Miles and Johnson published in 2014 concerning vaginal dilator therapy in women receiving pelvic radiotherapy found no reliable evidence that vaginal dilators prevent stenosis or improved sexual QOL.[51] Thus, the optimal treatment of vaginal stenosis including vaginal dilator therapy requires further investigation. In one study without dilator therapy, the majority of women experienced resolution of genital lesions whereas 4 of 32 women in the study by Hirsch et al required surgical intervention.[11] Three of these 4 women were diagnosed initially with higher-grade GVHD, indicating that severity is directly related to outcomes. Thus, early diagnosis and intervention may prevent the need for more invasive therapies such as surgery.

Recently, the International Consensus Project on Clinical Practice in Chronic GVHD committee published clinical guidelines for gynecologic care after HSCT.[52] The recommendations include local corticosteroids (class IV) as the mainstay therapy for genital changes. Surgical intervention may be necessary in severe cases (Table 1). Patients with genital atrophy appear to benefit from treatment with topical estrogen even if systemic hormonal therapy is initiated. In addition, because women are at an increased risk of developing squamous cell carcinoma of the cervix, annual Papanicolaou tests and pelvic examinations should be performed to monitor for changes. Ideally, these examinations may be performed by a member of the transplant team in collaboration with a dedicated gynecologist educated in GVHD.

Premature ovarian failure: The use of hormonal therapy in women after HSCT is best initiated early because many women develop premature ovarian failure (Table 1). Untreated premature ovarian failure can lead to an increased risk of osteoporosis, cardiovascular disease, and cognitive impairment. Thus, the International Consensus Project on Clinical Practice in Chronic GVHD recommends systemic hormonal therapy in women aged <40 years regardless of symptoms. Early initiation of hormone therapy is associated with a reduced cardiovascular risk, whereas delayed treatment may increase cardiovascular risk.[53] Studies have shown that the risk of breast cancer in patients initiating hormonal replacement therapy before age 40 years is not increased compared with normal menstruating women.[54]

Infertility: Given the high risk of infertility, counseling and fertility management are an integral part of the transplant process and are best addressed by a reproductive endocrinologist or a gynecologist with expertise in this area. There is promising research by Blumenfeld et al and a systemic review by Bedaiwy et al for gonadotropin-releasing hormone agonist administration in conjunction with chemotherapy among patients with

lymphoma for the preservation of fertility.[55,56] In addition, in vitro fertilization, embryo cryopreservation, oocyte cryopreservation, and ovarian tissue banking are important to consider for fertility preservation.[27] In men, sperm banking is preferred for fertility preservation.

Genital changes in men: In male patients with inflammatory genital changes, once-daily or twice-daily high-potency topical corticosteroids (class III/IV) were used with good resolution of symptoms (Table 1).[12] Genital lichen sclerosis can benefit from short-term topical calcineurin inhibitors.

Male hypogonadism: In several studies, patients with hypogonadism were treated with testosterone replacement therapy (TRT).[32–34] Patients with diminished libido were found to have an improvement in their symptoms but patients with ED had equivocal responses with TRT (Table 1). Thus, patients with low libido and low-to-normal levels of testosterone may benefit from TRT. However, given the controversial evidence regarding the effect of TRT on prostate cancer, it is important to monitor patients closely for signs of prostatic hyperplasia, especially among the elderly. In addition, the majority of males recovered normal testosterone levels and sexual function within a year after HSCT, and therefore the risks of TRT may outweigh the benefits.[26] Clinicians should also be cautious when using TRT in those patients who have developed secondary iron overload due to pretransplant transfusions because TRT can increase the risk of complications as a result of secondary polycythemias.[57] Patients who are likely to have arteriogenic insufficiency may improve with a vasodilator such as a phosphodiesterase inhibitor or a smooth muscle relaxant.[32]

Medications—Steroid immunosuppressants, proton pump inhibitors, antidepressants, opioids, anxiolytics, hormone replacement therapy, antihypertensive drugs, and statins are some of the most commonly prescribed medications after HSCT. Many of these medications may contribute to sexual dysfunction due to drug-drug interactions, pill burden, and combined side effect profiles (Table 1). Periodic review and elimination of polypharmacy as much as possible is a key principle to reduce sexual side effects.

Future Directions

Awareness and the early diagnosis of sexual dysfunction related to conditioning regimens, medications, and GVHD are important for QOL in long-term survivors of HSCT. The assessment of pretransplant sexual function and regular assessment after transplantation enables the early identification of changes warranting treatment. Longer-term follow-up after HSCT would also be valuable, because to the best of our knowledge the majority of studies to date have only followed patients for 2 to 3 years.[58] There appears to be a general lack of training for physicians and allied health professionals to adequately address such issues with patients and their partners. Thus, there needs to be training in how to initiate discussions regarding sexual dysfunction because it often is a difficult topic for patients to discuss with their physicians.

There is promising evidence for multiple medical and behavioral treatment options for patients after HSCT. To address the effectiveness of these treatments, further evaluation

through prospective studies should be performed. Patients, their partners, families, and physicians would all benefit from discussions relating to potential side effects and treatment opportunities.

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TABLE 1

Risk Factors for Sexual Dysfunction and its Consequences and Possible Interventions

Risk factors	Effects	Consequences on sexual function	Possible interventions
TBI	-gonadal failure -infertility -vulvar or vaginal dryness -penile dryness	decreased libido, arousal and orgasm, discomfort during intercourse erectile dysfunction in males performance stress vulvar or vaginal dryness -penile dryness	hormonal replacement erectile dysfunction medication management of stress and relationship issues vulvar or vaginal dryness -penile dryness
GVHD	-vulvar or vaginal dryness -penile dryness -inflammatory changes -vaginal narrowing, -vulvar or vaginal scarring, stenosis	pain during intercourse; abnormal ejaculation in males pain during intercourse; abnormal ejaculation in males pain; at extreme, impossibility to have intercourse	lubrication during intercourse local therapy use of vaginal dilator therapy, ultralow dose estrogen vaginal ring
Medications and drug interactions	-antidepressants -antipsychotic medications -beta-blockers	negative effect on libido, arousal and orgasm vaginal dryness	consider options for reducing the dose or finding an effective alternative medication
Chronic medical problem (burden of health conditions)	-CV complications -diabetes -chronic GVHD -secondary cancer -fatigue	decrease of sexual interest erectile dysfunction in males	treatment of underlying medical problems
Psychological distress	-personal well-being and partner relationship -feeling unattractive after HSCT	decrease of sexual interest, negative effect on libido, arousal and orgasm	psychotherapy sex therapy

Abbreviations: CV: cardiovascular; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation.