

transplant therapy, and conditioning regimen.⁶⁵ Although the risk of gonadal failure is high in all individuals, women generally experience higher rates of failure than do men.

Women are at high risk of hypergonadotropic hypogonadism after HCT.⁶⁶ Hypogonadism is nearly universal after high dose irradiation or busulfan. Risk is lower with cyclophosphamide alone. In general, ovarian endocrine failure is irreversible in adult women, but younger women, particularly prepubescent girls, have a better opportunity for recovery of gonadal function.

Fractionation of radiation reduces the risk compared with unfractionated radiation. Prepubertal girls should be monitored closely for onset of puberty and, if puberty is not experienced by age 12 to 13, be referred for full endocrinology evaluation and consideration of hormone supplementation. Adult women should be evaluated by a gynecologist and may require hormone replacement therapy to maintain libido, sexual function, and bone density. Libido is often decreased and only partially corrected by hormone replacement therapy in women. Vaginal GVHD may result in strictures and synechiae. Supplemental vaginal lubrication is available and should be discussed by the treating physician.

Most men have normal testosterone levels after transplantation, although germ cell damage (infertility) is a near-universal finding in men exposed to high doses of radiation or chemotherapy. Most reports suggest that prepubertal boys experience normal puberty and demonstrate normal testosterone levels following HCT.⁶⁶ Testing and consideration of hormone replacement therapy for men is recommended based on symptoms. Failure to progress through puberty in a timely fashion should prompt referral for a full endocrinology evaluation.

Transplant recipients have a low incidence of primary adrenal failure after HCT. Chronic therapy with corticosteroids for GVHD will suppress the pituitary-adrenal axis, but function usually recovers gradually once exogenous corticosteroid exposure ends. Greater length and intensity of exposure is generally associated with longer persistence of adrenal suppression. Patients with prolonged exposure to corticosteroids after HCT should have adrenal axis testing when withdrawing corticosteroids, particularly if symptoms of adrenal insufficiency develop. Clinicians should maintain awareness of possible hypoadrenalism in patients receiving long term corticosteroids who develop acute illness and consider 'stress dose' corticosteroids.

Growth in children may be adversely affected by HCT, depending upon their pre-transplant therapy and conditioning regimen.^{65,66} A large body of data suggests that radiation is associated with growth defects in children who receive HCT. Cranial radiation, in particular, increases the risk of diminished growth in children. Some reports suggest that chemotherapy alone may cause growth deficiencies. Growth is a complicated process and may be adversely impacted by many additional factors, including general illness, nutritional deficits, hormonal deficiencies, long-term corticosteroids, and GVHD. The risk of impaired growth is greatest in the youngest children. Children should be closely monitored for appropriate growth velocity after HCT. A pediatric endocrinologist should evaluate children who do not achieve adequate growth, and assessment of growth hormone levels should be considered. Growth hormone deficiency following TBI has been demonstrated in some studies, but not in others. Since growth failure is likely to be multifactorial, consideration must be given to causes other than inadequate growth hormone. The benefits of growth hormone supplementation are unclear. However, in children with demonstrated deficiency, supplementation is commonly prescribed.

Recommendations

- Thyroid function tests (TSH, T3, and free T4) should be performed at 1 year and yearly thereafter in all transplant recipients and additionally if relevant symptoms develop.
- Clinical and endocrinologic gonadal assessment at 1 year after HCT is recommended for all women who were post-pubertal at the time of transplantation. Frequency of subsequent assessments should be guided by clinical need (e.g., menopausal status). Women should have annual gynecologic evaluation as part of general health screening, at which time, hormone replacement therapy should be addressed for those who are post-menopausal.
- Gonadal function in men, particularly FSH, LH, and testosterone, should be assessed if symptoms warrant (lack of libido or erectile dysfunction). Consider referral to an endocrinologist for men who may need testosterone replacement therapy.
- Clinical and endocrinologic gonadal assessment of pre-pubertal boys and girls should be initiated 6–12 months after transplantation, with further follow-up schedule determined in consultation with an endocrinologist.
- Patients withdrawing from prolonged corticosteroid usage should have slow terminal tapering of corticosteroids; stress doses of corticosteroids may be warranted during acute illness in patients who have been on chronic corticosteroids in the past.
- Growth velocity should be monitored every year in all children, with assessment of thyroid function and growth hormone if growth velocity is abnormal.

MUCO-CUTANEOUS COMPLICATIONS

Late complications involving skin and appendages are frequent after HCT.⁶⁷ Nearly 70% of patients with chronic GVHD experience skin involvement. Early changes of lichen-planus like or papulosquamous lesions may progress to sclerosis or poikiloderma and can be associated with skin ulcers and subsequent infections. Alopecia, thinning of scalp hair, nail dystrophy, sweat impairment and skin dyspigmentation are common complications after chronic GVHD.

HCT survivors, especially recipients of allogeneic HCT, are at risk for developing secondary cancers of the skin.²⁴ Patients should be counseled about early detection and prevention of skin cancers including avoiding excessive sun exposure, using adequate skin protection and periodic self examination of the skin with prompt referral to a dermatologist for further evaluation and treatment of suspicious skin lesions.

Severe genital GVHD may develop in approximately 12% of women with or without associated systemic GVHD.^{68,69} Patients may present with excoriated or ulcerated mucosa, fissures, narrowing of introitus, or vaginal scarring and obliteration that may lead to hematocolpos. Initial symptoms may be mild and nonspecific such as dryness, dyspareunia or post coital bleeding and if not recognized they may lead to important sexual dysfunction. Careful questioning and examination should be performed as patients without sexual activity may not detect these abnormalities and sexually active patients may not disclose relevant symptoms. Biopsy may be needed to establish the diagnosis. Care should be taken when reducing systemic immunosuppression as reactivation of genital GVHD may occur. Vaginal strictures may limit the performance of routine Papanicolaou smears as well as sexual intercourse. Treatment of vaginal GVHD includes topical steroids, topical cyclosporine and vaginal dilators. Surgical intervention can be used to treat severe cases. In contrast to

chronic GVHD, patients with hypo-estrogenism due to premature menopause may present with thin and pale vulvar mucosa that responds well to lubricants and topical estrogens. However, patients may have changes due to GVHD and hypo-estrogenism concurrently. Genital involvement with GVHD is less common in men and may result in phimosis.

Recommendations

- Patients should perform routine self examination of the skin and avoid excessive exposure of sunlight without adequate protection.
- All women recipients of allogeneic HCT should have clinical screening for symptoms of genital GVHD. Women who have established chronic GVHD should have gynecological exam to screen for genital involvement.
- Patients should be counseled about self examination of the vaginal area, general hygiene measures, and early recognition of local symptoms. Application of topical vaginal immunosuppressive agents, such as ultrahigh potency corticosteroids or calcineurin inhibitors, prescription of systemic hormonal replacement therapy if indicated, and the use of vaginal dilators should be initiated early in the course of the disease.

SECONDARY CANCERS

Second malignancies after HCT are a devastating late complication. Patients receiving allogeneic HCT have a 2 to 3 fold increased risk of developing solid tumors, compared to an age-, gender-, and region-adjusted population.⁵⁹ Nearly all cancer types are described after allogeneic and autologous transplant, including oral cancers, as mentioned above. Risk factors include radiation therapy, length, and intensity of immunosuppression and chronic GVHD.²⁶ However, a recent long-term follow-up analysis of patients transplanted after myeloablative doses of busulfan and cyclophosphamide found similar increased risk.²⁵ Risk increases with time after transplantation, particularly for radiation-related malignancies. Recent analyses suggest that risk of radiation-related (sarcoma, breast and thyroid cancers) and non-radiation related (squamous cell carcinoma linked to chronic GVHD) solid tumors continues to increase beyond 10-years post transplantation.^{24,26} Children who have received cranial irradiation are at risk for developing brain tumors. HCT recipients with Fanconi's anemia are also at risk for developing oro-pharyngeal cancers. Providers can consider vaccination against human papilloma virus according to country-specific general population recommendations.¹⁰ All patients should at least receive country-specific general population recommendations for screening for cancers. Screening for breast cancer is recommended at an earlier age (25 years or 8 years after radiation, whichever occurs later) but no later than age 40 among recipients of TBI or chest irradiation. Early referral to a dermatologist should be considered in patients with skin lesions suspicious for cancer.

Risk of secondary leukemia or myelodysplasia after autologous HCT is also higher than anticipated, with an overall incidence of about 4% at 7 years after transplantation; with a median onset of 2.5 years (range, 3 months to 7 years) post-transplantation. Risk appears to be increased for patients receiving prior alkylator therapy, prolonged administration of conventional chemotherapy, and higher doses of pre-transplant irradiation.⁷⁰

Post transplant lymphoproliferative disorders (PTLD) are a rare complication of allogeneic HCT associated with greater donor-recipient HLA disparity, T cell depletion and GVHD.⁷¹ Overall incidence is 1% at 10 years after HCT. Although these usually occur early (within 6 months of transplantation), PTLD is reported as late as 8 years after HCT. The majority of PTLD are associated with Epstein-Barr Virus (EBV) infection. Quantitative PCR detection

of EBV reactivation allows prompt initiation of anti-CD20 monoclonal antibody therapy before development of frank PTLD.⁵⁹

Recommendations

- Exposure to radiation, and photosensitizing effects of many commonly used transplantation-related medications increases the risk of skin cancers among HCT recipients. All HCT recipients should be encouraged to reduce UV skin exposure through use of high SPF sunscreens or skin coverage.
- All patients should be advised of the risks of secondary malignancies annually and encouraged to routinely perform recommended screening self-examination such as genital/testicular and skin examination. Women should discuss breast self-examination with their physicians. All patients should be encouraged to avoid high-risk behaviors as recommended under General Health and Preventive Screening section, including avoidance of tobacco, passive tobacco exposure or excessive unprotected skin UV exposure.
- Screening clinical assessment should be performed yearly, and should include symptom review for secondary malignancies. Clinical examination and screening for secondary malignancies should follow the recommendations outlined under the General Health and Preventive Screening section. In women with radiation exposure (e.g. TBI or radiation to the chest region), initiation of screening mammography should occur at age 25 or 8 years after radiation, whichever occurs later, but no later than age 40 years. Particular attention to oral malignancies should be paid to patients with previous severe chronic GVHD of the oral and pharyngeal mucosa.

PSYCHOSOCIAL ADJUSTMENT AND SEXUAL COMPLICATIONS

Depressive symptoms and psychological distress are frequently observed in HCT survivors. Fatigue, anger, insomnia, and problems with marital relationships may also be seen. Pediatric patients may experience altered behavior patterns, changes in social habits, and changes in academic/school behavior. At the transition from acute convalescence to long-term follow-up, psychological distress may increase rather than abate as the patient and his/her family must cope with changes in roles, employment situations, and financial difficulties. Spouses and other caregivers may also exhibit high levels of depression and psychological distress. They often report loneliness and low levels of perceived social support. Children may suffer from separation from one or both parents and the consequences of stress and upheaval in the family. At a minimum, screening for depression is recommended every 6–12 months after transplantation as per the general health maintenance section below. Specific tools for screening for psychosocial difficulties after HCT are also available and could be used with a similar frequency to depression screening. Sexual dysfunction occurs in a significant number of survivors and may be multifactorial in origin, from depression to gonadal hormonal deficiency.

Recommendations

- A high level of vigilance for psychological symptoms should be maintained. Clinical assessment is recommended throughout the recovery period, at 6 months, at 1 year, and at least yearly thereafter, with mental health professional assessment recommended for those with recognized deficits.
- Inquiry as to the level of spousal/caregiver psychological adjustment and family functioning should be performed at regular intervals.

- In adults, sexual function should be queried at 6 months, at 1 year and yearly thereafter (also see section on Muco-Cutaneous complications).

FERTILITY

Male and female HCT survivors are at risk for infertility secondary to pre-transplant and transplant related treatment exposures.^{72,73} Among transplant survivors of the child bearing age group, loss of fertility can be associated with psychological consequences that can affect quality of life. Conditioning regimens with TBI or busulfan plus cyclophosphamide can cause gonadal failure, although risk may be lower with regimens that include cyclophosphamide only. Older age at transplant and chronic GVHD are associated with low likelihood of gonadal recovery. Non-assisted natural pregnancies following gonadal recovery in women or in partners of male transplant recipients have been reported, but the estimated incidence is less than 15%.

The outcome of pregnancy after transplantation is generally good, although women are at increased risk of fetal and maternal complications and post-transplant pregnancy should be considered a high-risk pregnancy.⁷³ The incidence of congenital anomalies is not higher than in the normal population and the rate of miscarriage is not increased. Women exposed to TBI have a higher than normal incidence of preterm deliveries and low or very low birth weight infants. Irradiation may result in uterine vessel damage and reduce uterine volume.

A general recommendation is to delay spontaneous or assisted pregnancies for at least two years after HCT since this is the period of highest risk of relapse after transplantation. Contraception counseling in survivors after HCT with gonadal recovery is recommended and contraception is advisable if fertile or if fertility status is not known and pregnancy is not desired. Even if infertile, barrier contraception is recommended with new partners to prevent sexually transmitted diseases.

Women with gonadal recovery should also be advised about the risks of premature menopause.

Recommendations

- Consider referral to appropriate specialists for patients who are contemplating a pregnancy or are having difficulty conceiving.
- Although infertility is common, patients should be counselled regarding birth control post-transplantation.

GENERAL SCREENING AND PREVENTIVE HEALTH

In addition to transplant-specific risk factors mentioned above, HCT survivors face general risks found in the non-transplanted population. In general, transplant survivors should be under the care of physicians comfortable with providing care for general health and hematology-oncology specific issues. Summarized below are screening and lifestyle recommendations for the general adult population that are also relevant for HCT survivors. Further details about screening recommendations for adults and children can be found at: <http://www.uspreventiveservicestaskforce.org>.^{74,75}

Recommended screening for all patients

- Hypertension: Blood pressure should be checked at least every 2 years. In children, hypertension is defined as readings greater than the 95th percentile for age, sex and height. Treatment is indicated for readings of greater than 140/90 in adults on two separate visits at least 1 week apart, unless hypertension is mild or

can be attributed to a temporary condition or medication (e.g., cyclosporine). Non-pharmacologic treatments may also be tried for mild hypertension and include moderate dietary sodium restriction, weight reduction in the obese, avoidance of excess alcohol intake, and regular aerobic exercise.

- **Hypercholesterolemia:** Cholesterol and HDL levels should be checked every five years starting at age 35 for men and 45 for women. Screening should start at age 20 for anyone who smokes, has diabetes, hypertension, obesity (body mass index ≥ 30 kg/m²), or a family history of heart disease before age 50 for male relatives or before age 60 for female relatives. Fasting is not required for accurate measurement of cholesterol and HDL, but is required for LDL and triglycerides. As a rough guideline, total cholesterol levels >200 mg/dl (>5.0 mmol/l) or HDL levels <40 mg/dl (<1 mmol/l) should be followed up by a full fasting lipid panel. Treatment goals are based on overall risk of heart disease (e.g., greater than a 10% chance of coronary heart disease in 10 years). Overall risk assessment will include the following risk factors: age, sex, diabetes, clinical atherosclerotic disease, hypertension, family history, low HDL (<40 mg/dl or 1.0 mmol/l), and smoking. An online calculator is available at <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>.
- **Colorectal cancer:** Screening should start at age 50 in the absence of a family history (first degree relative diagnosed with colorectal cancer before age 60). The interval of testing depends on the type of testing procedure and the prior screening results. There are several screening approaches including annual fecal occult blood testing (3 cards at home), sigmoidoscopy every 5 years with fecal occult testing every 3 years, or colonoscopy every 10 years. Virtual computerized tomography is a new method, currently under investigation. No one approach alone or in combination has proven superior, however a single digital rectal exam with occult blood testing is not recommended.
- **Diabetes:** Screening for type 2 diabetes is indicated for people every three years after age 45 or in those with sustained higher blood pressure ($>135/80$) because blood pressure targets are lower for diabetics. A fasting plasma glucose > 126 mg/dl (>7 mmol/l), confirmed by testing on another day, is diagnostic for diabetes.
- **Depression:** Asking two simple questions about mood and anhedonia ("Over the past 2 weeks, have you felt down, depressed, or hopeless?" and "Over the past 2 weeks, have you felt little interest or pleasure in doing things?") is probably as effective as longer screening tools. Frequency of screening is not stated, but it is reasonable to screen every 6–12 month post-transplantation or as clinically indicated. Affirmative answers to the questions above should trigger in depth evaluation for depression to determine the need for pharmacological or psychotherapeutic treatments.
- **Sexually transmitted diseases:** Chlamydia screening is recommended for women under the age of 25 who are sexually active. Screening and appropriate treatment decrease the incidence of pelvic inflammatory disease and pregnancy-related complications, although most women will be infertile after myeloablative transplantation. Male and female survivors should be reminded that protection against sexually transmitted disease is important even when pregnancy is unlikely or impossible.

Sex-specific recommendations

Recommended screening for men:

- Prostate cancer: There is no consensus about the use of prostate-specific antigen or digital rectal examination for prostate cancer screening.

Recommended screening for women:

- Breast cancer: Screening with mammograms should start at age 40 and occur every 1–2 years. Breast self-exam is not recommended. In women exposed to > 800 cGy radiation, screening should start at age 25 or 8 years after radiation exposure, whichever is later but no later than age 40, based on the data from Hodgkin lymphoma survivors.
- Cervical cancer: Screening with pap smears should be performed every 1–3 years in women older than 21 or within three years of initial sexual activity, whichever occurs earlier.
- Osteoporosis: Screening with a bone density test should start at age 65 for women in the general population, or if the individual's fracture risk is equivalent to a 65 year old woman (9.3% risk at 10 years).⁷⁶ An online calculator is available to determine the 10 year risk of fracture (www.shef.ac.uk/FRAX/). Also see section on Skeletal Complications for additional recommendations for HCT recipients.

Healthy lifestyle recommendations for all patients

- Eat a healthy diet with a wide variety of foods.
- Don't smoke (passive or active exposure), chew tobacco or use illegal drugs.
- Use alcohol in moderation, generally less than 2 drinks per day.
- Maintain a healthy weight.
- Avoid excessive sun exposure and wear sunscreen protection for anticipated periods of long exposure.
- Follow general population age specific guidelines for physical activity (www.health.gov/paguidelines).⁷⁷ Adults (aged 18–64) should do 2 hours and 30 minutes a week of moderate-intensity, or 1 hour and 15 minutes a week of vigorous-intensity aerobic physical activity or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 minutes. Adults should also do muscle strengthening activities that involve all major muscle groups performed on 2 or more days per week.

IMPLEMENTATION OF GUIDELINES IN RESOURCE LIMITED COUNTRIES

Although the Working Group has provided recommendations that should be applicable to all HCT recipients, they recognized that resource constraints may limit their implementation, especially in certain geographic regions and developing countries. Some examples of such challenges include availability of specialists with expertise and experience in managing post-transplant complications and availability of tests and procedures. Furthermore, issues related to healthcare access (e.g., distance to transplant center or health care facility with adequate expertise and resources) may restrict the ability of some patients to obtain screening and preventive care. In circumstances where resource limitations do not allow for comprehensive evaluation and followup, health care providers should use their best clinical judgment in determining appropriate preventive care for HCT survivors based on their individual exposures and risk-factors for long-term complications.

LONG TERM FOLLOWUP OF HCT RECIPIENTS

To facilitate transition of HCT recipients from one phase of post-transplant care to another, transplant providers should provide HCT recipients with a survivorship care plan that includes a treatment summary and a followup care plan. This document can serve as an instrument for reminding providers about appropriate surveillance for late complications based on an individual patient's risk-factors and exposures. Since survivors can be at risk for late relapse, the care plan should also include appropriate followup for the disease for which HCT was performed. Survivorship care plan instruments that are specific to HCT recipients are lacking. Until they are routinely available, providers can consider instruments that have been developed for cancer survivors in general (e.g., LIVESTRONG Care Plan [www.livestrongcareplan.org], Passport for Care® [www.txch.org/passportforcare]). In addition, providers can consider incorporating the patient version of these guidelines (available at www.marrow.org) into a survivorship care plan document for HCT recipients.

Long-term survivors of HCT may not receive care at their transplant center. Because of patient or center preference, absence of immediate transplant related complications, or distance from the transplant center, transplant recipients may transition their care back to their hematologist-oncologists, primary care physicians or other health care providers. With an increasing number of transplant survivors, it is likely that non-transplant health care providers will play a greater role in survivorship care and may need to be aware of the unique exposures, risk factors and medical issues these patients face. The working group recognized that the models and primary site for long-term followup will vary by country and available resources. On occasion, adherence to particular recommendations may be inconsistent with national or regional guidelines, the availability of specific procedures or medications, or local epidemiological conditions. Individual clinicians should practice best clinical judgment in implementing these guidelines and when caring for an individual patient, should consider age, gender, coexisting comorbidities, cancer and transplant related exposures and immediate side effects in determining patient risks for specific long-term complications. Prevention, screening and management of late complications of transplantation may require a multidisciplinary approach, with involvement of the transplant center, oncologists, subspecialists, primary care physicians, and other health care providers, as necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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