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Care of the Adult Hodgkin Lymphoma Survivor

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Abstract

Of those individuals diagnosed with Hodgkin lymphoma, 85% will survive and may be affected by residual effects of their cancer and its therapy (chemotherapy, radiation therapy, stem cell transplantation). Hodgkin lymphoma survivors are at risk of developing secondary malignancies, cardiovascular disease, pulmonary disease, thyroid disease, infertility, premature menopause, chronic fatigue, and psychosocial issues. These conditions usually have a long latency and therefore present years or decades after Hodgkin lymphoma treatment, when the patient's care is being managed by a primary care provider. This review summarizes these unique potential medical and psychological sequelae of Hodgkin lymphoma, and provides screening and management recommendations.

Keywords

Hodgkin lymphoma; survivors; primary care physicians

Introduction

Hodgkin lymphoma is a highly curable malignancy; today 85% of patients with Hodgkin lymphoma become long-term survivors.(1) Because Hodgkin lymphoma tends to affect

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younger individuals, these patients have many life years ahead of them in which to experience the residual effects of Hodgkin lymphoma and its therapy. Survivors not only have increased long-term mortality, primarily a result of an excess of secondary malignancies and cardiovascular disease,(2) but also suffer from a high prevalence of other medical and psychosocial conditions that affect their health-related quality of life.

Follow-up of Hodgkin lymphoma survivors includes identification of disease relapse, management of persistent treatment side effects, and preventing and detecting potential late sequelae of therapy. This is challenging. There are no widely accepted guidelines for screening and management. In addition, the pattern of healthcare delivery in Hodgkin lymphoma survivors is variable. After treatment, patients are usually followed by their hematologist/oncologist for 5 years. At that point, primary care providers assume responsibility for ongoing management. However, many primary care providers and patients are not aware of the unique medical and psychological issues that Hodgkin lymphoma survivors may face. The goal of this review is to summarize the potential long term sequelae of Hodgkin lymphoma treatment and to provide screening and management recommendations.

Background: Treatment of Hodgkin lymphoma

The treatment of Hodgkin lymphoma has evolved over the past 50 years. In the 1960's, a staging laparotomy was routine, along with high-dose, extended field radiation therapy. The chemotherapy regimen MOPP (nitrogen mustargen, oncovin, procarbazine, and prednisone) was the standard for advanced stage disease in the 1970's. In the 1980's, laparotomy use became less common, and ABVD chemotherapy (adriamycin, bleomycin, vinblastine and dacarbazine) was used with increased frequency. Stem cell transplant for salvage therapy became available. In the 1990's, long term effects of therapy became increasingly apparent, and focus shifted to minimizing side effects while maintaining efficacy of treatment. Now patients with early stage disease are generally treated with combined modality therapy (low dose radiation and short-course chemotherapy), while those with advanced disease receive chemotherapy, generally ABVD, or a more intensive chemotherapeutic regimen BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone) for those with high risk disease.

Due to the evolution of treatment strategies, potential long-term treatment sequelae vary from patient to patient, depending on the year of treatment, type of chemotherapy, and dose and fields of radiation. Therefore, it is critical for both patient and health care providers to know the precise treatment details of each Hodgkin lymphoma survivor to better understand their individualized risk of long-term health conditions. Table 1 details key medical history in a Hodgkin lymphoma survivor. Ideally, this information should be communicated from the treating hematologist/oncologist in a treatment summary document.

Background: Long-Term Health Conditions

Secondary Malignancies

Secondary malignancies are the leading cause of morbidity and mortality among long-term survivors of Hodgkin lymphoma, primarily related to radiation therapy.(2, 3) There is an 18.5-fold increased risk of developing secondary malignancies in Hodgkin lymphoma survivors compared to the general population with a cumulative incidence of 11% at 20 years and 26% at 30 years.(4) After non-melanomatous skin cancers, lung, breast, and colorectal malignancies are the most common secondary malignancies(3), while sarcomas and non-Hodgkin lymphomas may also occur. Females have a significantly higher rate of secondary malignancies compared to males, largely due to breast cancer, with a cumulative

incidence of breast cancer of 13% at age 40 years.(5) Women treated with radiation in the adolescent years have a significantly higher risk of developing breast cancer than those treated later in life, although treatment-related premature menopause has been reported to have a protective effect against development of breast cancer.(6)

The latency period for secondary malignancies is variable. Chemotherapy related myelodysplasia and acute myelogenous leukemia occur within 10 years of treatment (median 3 years), and are more likely to be caused by alkylating chemotherapeutic agents such as those included in MOPP and BEACOPP as compared to ABVD. Radiation related solid cancers have a longer latency period (median, 14.3 years after treatment) with no plateau to the risk.(4)

Cardiovascular Disease (CVD)

Cardiac complications are primarily secondary to mediastinal irradiation, but patients exposed to anthracycline chemotherapy are also at risk for long-term cardiac toxicity. Most of the excess cardiac risk is not realized until 10 years after exposure, and the risk remains significantly elevated for at least 25 years. Traditional CVD risk factors are additive to this risk.

The primary cardiac complication and cause of excess mortality in Hodgkin lymphoma survivors is coronary artery disease (CAD). In a prospective study of asymptomatic Hodgkin lymphoma survivors treated with >35Gy of mediastinal radiation (mean 15 years after treatment), 7.4% of those screened had significant CAD on coronary angiography. With an additional 6.5 years of follow-up, 9.5% developed symptomatic CAD, including 2 fatal myocardial infarctions.(7) In addition to direct toxicity of Hodgkin lymphoma therapy on the heart and blood vessels, the increased risk of CAD may also be mediated by accelerating the development of established CVD risk factors. Data in childhood Hodgkin lymphoma survivors suggest an increased risk of metabolic syndrome.(8)

Symptomatic anthracycline toxicity typically presents a year or more following treatment due to progressive left ventricular dysfunction and resultant congestive heart failure (CHF), generally seen when doses exceed 550 mg/m². However, even in lymphoma patients who received moderate dose anthracyclines, 27.6% were found to have subclinical cardiomyopathy at a median of 8 years following treatment, the long-term implications of which are unknown.(9) CHF may only become evident at times of increased workload, such as pregnancy, anesthesia, illness, etc.

The risk of clinically important valvular dysfunction in Hodgkin lymphoma survivors treated with radiation is 5% at 20 years.(10) The incidence of radiation-induced non-coronary vascular disease is 7% (stroke, transient ischemic attack, carotid or subclavian artery stenosis) at 20 years after treatment.(10) Radiation-induced vascular damage results in premature atherosclerosis, generally with a latency period of 10–15 years.(11) Any large or small vessel in the treatment field can be affected, most commonly the aorta, carotid, subclavian, axillary, and innominate arteries, and the renal and mesenteric vessels. Although radiation renders vessels more susceptible to further damage by traditional risk vascular factors, affected patients are often younger and without risk factors.(12)

Pulmonary Disease

Pulmonary toxicity is associated with radiation dose and volume of lung tissue exposed, as well as with the use of bleomycin chemotherapy, particularly doses >400 mg.(13) The risk of bleomycin toxicity is increased in smokers, patients with renal dysfunction, patients >age 70, and those treated with chest irradiation and/or stem cell transplant.(13) Potential late pulmonary effects include interstitial pneumonitis, pulmonary fibrosis, and acute respiratory

distress syndrome when exposed to high levels of oxygen and/or intravenous fluids during administration of general anesthesia.(14)

Thyroid Disease

Twenty to thirty percent of Hodgkin lymphoma survivors are affected by thyroid abnormalities, most commonly clinical or subclinical hypothyroidism.(15) Radiation causes direct vascular damage to the thyroid gland resulting in primary hypothyroidism. Indirect effects and central hypothyroidism via involvement of hypothalamic-pituitary axis are less common. Less common thyroid disorders that may affect Hodgkin lymphoma survivors include Graves' disease, benign adenoma, multinodular goiter, thyroiditis, and thyroid malignancies.(15)

Infertility and Premature Menopause

Fertility is important to Hodgkin lymphoma patients, since many are in their reproductive years. Pelvic radiation or total body irradiation used as a conditioning regimen for bone marrow transplant may cause infertility.(16) More commonly, chemotherapy can damage maturing sperm and oocytes, particularly the alkylating agents used in MOPP and BEACOPP chemotherapy regimens.(16),(17, 18) ABVD chemotherapy regimen does not appear to lead to permanently impaired gonadal function.(19)

Even if a patient retains fertility following treatment, women may suffer from premature menopause (loss of ovarian function prior to age 40). In a study of 66 Hodgkin lymphoma patients treated from 1975–1990, 50% of women had premature ovarian failure and 65% of men had gonadal dysfunction.(20) As a result of premature menopause, women are susceptible to menopausal symptoms and sequelae at a younger age, including osteoporosis, heightened risk of CVD, vaginal dryness, decreased sexual desire, and hot flashes.

Fatigue

Chronic fatigue is common among Hodgkin lymphoma survivors, impacting up to 37% of patients,(21) and can persist long after treatment is completed.(22) The etiology of the fatigue remains unclear. An association has been demonstrated between fatigue and pulmonary dysfunction, but not cardiac or thyroid complications.(23) Another mechanism may be altered immune activity resulting in cytokine alterations that induce fatigue.(24)

Psychosocial Issues

Patients who survive major illnesses may have residual psychosocial complications. A study of psychological distress revealed that survivors of hematological malignancies (including Hodgkin lymphoma) were 1.6–1.7 times more likely to report depressive symptoms and somatic distress than their siblings.(25)

Anxiety has been identified as a significant issue in Hodgkin lymphoma survivors. In a cross-sectional survey of 459 patients in Norway, 14.5% were found to have anxiety symptoms, which is significantly higher than the general population (3.3%).(26) Predictors for anxiety included low education, combined chemotherapy and radiotherapy, and time since diagnosis ≥ 7 years.

Lymphoma survivors are as likely to have symptoms of post-traumatic stress disorder (PTSD) as subjects who experienced other highly stressful life events, such as loss of a spouse or serious motor vehicle accident.(27) In a cross-sectional study of 886 lymphoma survivors, 8% met the full PTSD diagnostic criteria, 9.1% met partial criteria, and a total of 39% of the sample met criteria for at least one PTSD symptom cluster compared to 2.4%

prevalence of PTSD in the general adult population.(28) Conversely, other survivors may experience a renewed positive outlook on life.

Recommendations for Follow-Up Care

Providing optimal long term medical care to Hodgkin lymphoma survivors is made more challenging by the lack of evidence-based guidelines, the temporal and individual variations in Hodgkin lymphoma treatment regimens, and the fact that many patients and their health care providers are unaware of their elevated long term health risks. Many of the recommendations for follow-up care are based on expert opinion. Therefore, medical decisions should be individualized for each patient based on their exposure to chemotherapeutic agents and/or radiation therapy and the time since treatment. See table 2 for a summary of follow-up care recommendations. In general, all cancer survivors should receive general health maintenance per standard recommendations based on age and then, depending on individual factors, additional or more frequent screening and preventive measures. All patients should be educated regarding the risk of late effects and advised to practice a healthy lifestyle (avoid tobacco, alcohol, and excess sun exposure and maintain a healthy weight via diet and exercise).

Vaccinations

All patients should have an annual inactivated influenza shot. Patients who had splenectomy or splenic radiation should have received the meningococcus, hemophilus influenzae type B (Hib) conjugate, and pneumococcal vaccine at the time of treatment, and be revaccinated with the pneumococcal vaccine once after 5 years.(29) Hematopoietic stem cell transplant recipients lose immune memory and therefore need to be revaccinated (see table 2 for detailed recommendations). Patients with a history of lymphoma should not receive live vaccines, including the nasal-spray influenza vaccine and herpes zoster vaccine, due to theoretical risk of altered immunocompetence.(29)

Secondary Cancers

Although it is estimated that almost half of the secondary malignancies can be detected at an early stage by periodic surveillance, evidence suggests that many of these high risk patients are not getting appropriate cancer screening.(30)

If a patient has undergone radiation therapy, in addition to counseling on sun protective measures, it is recommended that patients perform a monthly skin self-exam and have a yearly dermatologic exam with special attention to skin lesions and pigmented nevi in the radiation field.(31)

For female patients treated with chest or axillary radiation therapy (≥ 20 Gy) between ages 10–30 years, monthly self breast exams are recommended beginning at puberty. Annual clinical breast exams are recommended beginning at puberty and increasing to twice yearly after age 25 years. Annual mammography and consideration of breast MRI is recommended beginning 8 years after chest or axillary radiation or at age 40 years, whichever occurs earlier.(30, 31) Although expensive, one advantage of performing breast MRI is that it avoids the use of additional ionizing radiation in these young patients.

Colorectal cancer screening should be started 15 years after treatment or at age 35 for those survivors who have had pelvic or abdominal and/or spinal irradiation of doses greater than 30 Gy.(30, 31) Results from the initial colonoscopy should then inform the frequency of subsequent screening.

Lung cancer screening is more controversial in the Hodgkin lymphoma survivor. In our practice, we recommend history and physical exam surveillance annually for those who received chest radiation, with imaging reserved for those with concerning signs or symptoms. Counseling for smoking cessation is imperative as tobacco use increases the already elevated risk of lung cancer in these patients by more than 20-fold.(32)

Cardiovascular Disease

The accelerated atherosclerosis associated with radiation and chemotherapy should be addressed by early and aggressive screening and management of modifiable risk factors. All individuals should receive annual cardiovascular risk assessments that include a review of lifestyle practices and measurement of blood pressure and body mass index with appropriate counseling and management as indicated. Lipid screening starting at age 20 and every 3 years thereafter is cost-effective and improves survival in this patient population.(33) Baseline stress test and echocardiogram at 10 years can be considered.(34) Maintaining a high index of suspicion and prompt evaluation of symptoms of ischemia, left ventricular dysfunction, or pericardial disease is important, since early treatment can favorably modify prognosis. Valvular heart disease should be suspected when a patient with a history of mediastinal irradiation presents with dyspnea or effort intolerance, especially when a cardiac murmur is present, and warrants further assessment with echocardiography. Asymptomatic left ventricular dysfunction is common after anthracycline and radiation therapies and can progress over time, particularly in the setting of hypertension. Early identification of abnormalities in left ventricular dysfunction with screening echocardiography allows initiation of standard heart failure therapy, even in the asymptomatic patient. These measures have been shown to be effective treatment for symptomatic disease and a number of studies have found that early treatment may prevent progression.(35)

Patients with a history of radiation exposure should be evaluated for signs and symptoms suggestive of peripheral vascular disease. A detailed vascular examination (palpation of peripheral pulses, auscultation for bruits) should be included as part of an annual physical examination, paying close attention to the previously radiated fields. If there are abnormalities, ultrasound and vascular lab studies are indicated with referral to a vascular specialist. Smoking is associated with a 3-fold excess risk of stroke in Hodgkin lymphoma survivors, emphasizing the importance of counseling these patients on smoking cessation. (30)

Pulmonary Disease

Patients should not smoke. Physicians should inquire about the history of bleomycin exposure, as this would be important information should the Hodgkin lymphoma survivor require surgery. It is recommended that oxygen exposure and intravenous fluids be minimized in the perioperative period.(14) Scuba diving should generally be avoided in those who suffered bleomycin lung toxicity or have abnormal pulmonary function testing post-treatment.(36)

Thyroid Disease

The high frequency of thyroid disorders in patients treated with radiation to the head and neck requires lifelong thyroid surveillance. Examination of the thyroid and thyroid stimulating hormone (TSH) should be checked on an annual basis. TSH levels above 5 Mu/litre, even if no overt clinical manifestations are present, warrant correction with thyroxine to minimize clinical symptoms and development of benign and malignant thyroid nodules. (37) Patients with a palpable nodule should have thyroid imaging with Doppler ultrasonography, with further management based on imaging findings.(38)

Infertility and Premature Menopause

The best time to address fertility issues is prior to initiation of Hodgkin lymphoma treatment, and referral to a reproductive specialist is recommended. However, this is not always possible due to the urgency of treatment and unfortunately, is frequently not offered. In these cases, referral to a reproductive specialist after treatment is recommended. Many Hodgkin lymphoma experts recommend waiting two years after Hodgkin lymphoma treatment to begin reproductive efforts when the risk of relapse significantly decreases.

Women treated with alkylating agents such as MOPP and BEACOPP should be monitored for premature menopause and initiation of calcium, vitamin D, exercise, and bisphosphonates for treatment of bone demineralization is recommended.(39)

Fatigue

Fatigue is a common and troubling symptom among survivors of Hodgkin's disease and can persist long after treatment ends. The etiology remains unclear, but reversible causes of fatigue, such as depression, thyroid, or cardiorespiratory disease should be excluded. From a management standpoint, both aerobic physical activity programs and correction of anemia have been shown to be effective in the treatment of cancer-related fatigue.(40)

Psychosocial Issues

Psychosocial issues may present themselves at any time during the period of survivorship, not just at initial diagnosis. These issues may persist for years following treatment. Patients should be asked about their psychosocial functioning, including financial concerns, social support, and return to work, school, or homemaking. Screening for anxiety and depressive symptoms should be performed. Referral to psychiatry or psychology, support groups, or social services may be useful in minimizing psychosocial distress.

Conclusion

Hodgkin lymphoma survivors are at increased risk of long-term health and psychosocial issues. These patients may be managed by a variety of health care providers over their lives. It is important that each patient's oncological treatment history is known and Hodgkin lymphoma survivors are monitored for potential late sequelae of treatment.

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Table 1**Key Medical History Information in Survivors of Hodgkin Lymphoma**

Age at diagnosis
Diagnosis date
Stage at diagnosis
Radiation Therapy <ul style="list-style-type: none"> • Treatment field(s) • Total radiation dose • Dates of treatment
Surgery <ul style="list-style-type: none"> • Splenectomy
Chemotherapy <ul style="list-style-type: none"> • Treatment regimen • Total dose(s) <ul style="list-style-type: none"> ◦ Bleomycin ◦ Anthracyclines • Dates of treatment
Bone marrow/stem cell transplantation <ul style="list-style-type: none"> • Conditioning regimen (chemotherapy, radiation with total dose and fields) • Autologous or allogeneic transplant • Consolidation radiation post-transplant
Serious toxicities during treatment
History of blood transfusion and date(s)
Vaccination record
History of other malignancies
Reproductive/menstrual history
Mental health <ul style="list-style-type: none"> • Depression • Anxiety
CVD risk factors (hypertension, hyperlipidemia, smoking, diabetes)
Family history of malignancy, CVD, thyroid disorders

Table 2

Recommendations for Follow Up Care in HL Survivors.

Potential Long-Term Sequelae	Intervention	Frequency
General	Education regarding late effects	Annual
	Lifestyle counseling (smoking cessation, physical exercise, healthy diet, weight)	Each visit
Loss of Immunity	Vaccinations	
	<u>All patients</u>	
	Inactivated influenza	Annual
	<u>Splenectomy or splenic irradiation</u>	
	Meningococcus	At treatment
	Hemophilus influenza type B	At treatment
	Pneumococcal	At treatment and 5 years
	<u>Hematopoietic stem cell recipients</u>	
	Inactivated influenza	Annual starting 6–12 months post-transplant
	Hemophilus influenza type B	12, 14, and 24 months posttransplant
Secondary cancers	Pneumococcal	12 and 24 months posttransplant
	Tetanus-diphtheria-pertussis	12 months post-transplant
	Tetanus-diphtheria	14 and 24 months post-transplant
	Hepatitis B	12, 14, and 24 months post-transplant
	Inactivated polio	12, 14, and 24 months post-transplant
	Measles-mumps-rubella	24 months post-transplant
	*Live vaccinations contraindicated in all HL survivors	
	Skin cancer	
	<u>Treated with any radiation therapy</u>	
	Sun protection	
Breast cancer	Self-examination	Monthly
	Dermatology examination	Annually
	<u>If female treated with chest or axillary radiation ≥ 20 Gy between ages 10–30 years</u>	
	Self-examination	Monthly at puberty
	Clinical breast examination	Annually until age 25, then twice yearly
Colorectal cancer	Mammography	Annually beginning 8 years after radiation or at age 40, whichever comes earlier
	Breast MRI	Consider annually beginning 8 years after radiation or at age 40, whichever comes earlier
Colorectal cancer	<u>If treated with pelvic, abdominal, or spinal radiation ≥ 30 Gy</u>	

Potential Long-Term Sequelae	Intervention	Frequency
	Colonoscopy	15 years after treatment or at age 35, subsequent testing based on initial colonoscopy
Lung cancer	<u>If treated with chest radiation ≥ 30 Gy</u> History & physical examination Smoking cessation counseling	Annually Every visit
Cardiovascular disease	History and physical exam Cardiac Vascular (in radiation fields) Hypertension screening Lipid screening Echocardiogram Stress test	Annually Annually Each visit At age 20 and every 3 years Consider at 10 years if received anthracyclines or radiation Consider at 10 years if received radiation
Pulmonary disease	<u>If treated with bleomycin</u> Counseling regarding risk of oxygen, IV fluids	Perioperative
Endocrine dysfunction Thyroid disorders	<u>If treated with neck irradiation</u> Thyroid function screening and examination	Annually
Infertility	Referral to reproductive specialist	At diagnosis if possible
Premature menopause	Osteoporosis screening Calcium, vitamin D supplementation, exercise Rx	At cessation of menses then every 5 years Each visit for menopausal women
Psychosocial issues	Depression and anxiety screening	Annually or with symptoms

Note: Based on information from Center for Disease Control and Prevention, 2010; Landier W et al, 2007; Hudson MM et al 2009; Mauch P et al, 2005