Late Effects of Treatment for Hodgkin Lymphoma

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Abstract
With advances in multimodality therapy, survival from Hodgkin lymphoma (HL) now exceeds 80%, resulting in a large cohort of survivors who are at risk for adverse long-term sequelae of therapy. This risk is complicated by possible endogenous predispositions to developing late effects, which relate to the patient’s underlying susceptibility to HL. Finally, the impact of HL on the host can compromise organ function. This article reviews the possible dominant late effects for survivors of HL and strategies for monitoring and screening. As therapy for HL has changed and evolved, so has the spectrum of late effects. Mortality from HL has decreased, whereas delayed effects of therapy have increased. Refinements in therapy to decrease toxicity have occurred in response to the success in curing HL. Thus, modifications in therapeutic protocols using a risk-adapted strategy have reduced the use of alkylating agents, anthracyclines, and radiotherapy, which are associated with adverse long-term sequelae. The most clinically evident sequelae are those involving the endocrine and cardiovascular systems, and the most morbid are hematologic and solid second malignancies. Primary and secondary prevention strategies can be developed as knowledge of delayed effects of therapy increases. (JNCCN 2006;4:249–257)

Multimodality therapy for Hodgkin lymphoma (HL) had a 5-year relative survival of 85.3% from 1995 to 2001. However, this survival was accompanied by adverse long-term health-related outcomes that included second malignant neoplasms, organ dysfunction, and psychosocial sequelae.

Second Malignant Neoplasms
Several large studies have examined the incidence and spectrum of second malignant neoplasms (SMNs) in HL survivors. Reports from large cohorts showed a 7 to 18 times higher risk of subsequent malignancies compared with that of the general population. In an analysis of SMNs, a multicenter study of childhood cancer survivors found the highest reported standardized incidence ratio for secondary cancers (9.7) among survivors of HL. In those patients, HL was an independent risk factor for SMN even after adjusting for radiotherapy and chemotherapy exposures.

The risk for leukemia seems to plateau at 10 to 15 years after therapy, whereas the risk for second solid malignancies, including sarcoma, melanoma, and breast, lung, thyroid, and gastrointestinal cancers, increases with ongoing follow-up. Compared with adults, children may be more prone to developing subsequent malignancy because of growth potential and endogenous hormonal factors. In contrast, adult women may have a greater risk than adult men, even after accounting for breast cancer; however, this gender effect is not consistent among studies. In addition, patterns of second solid tumors differ among pediatric and adult survivors, with breast cancer being more common after childhood or young adulthood HL, when younger age at treatment is associated with increased risk, and lung cancers after adult HL. These second malignancies may be modified by health behaviors. For example, smoking further increases the risk of lung cancer.

Although recurrent disease seems to increase risk, probably because of the added burden of salvage therapy, experts disagree on whether stem cell transplantation...
increases risk over conventional retrieval therapy. However, in most reports the risk for SMN is elevated among patients who have undergone autologous stem cell transplantation for HL. Metayer et al. conducted a case-control study of 56 patients with secondary myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) and 168 matched controls within a cohort of 2,739 patients receiving autologous transplantations for HL or non-Hodgkin lymphoma. In multivariate analyses, risks for MDS/AML increased significantly with the intensity of pretransplantation chemotherapy and with mechlorethamine- or chlorambucil-based therapy, compared with cyclophosphamide-based therapy. Leukemia risk did not seem to increase with lower-dose total body irradiation (≤12 Gy), but did elevate with higher doses (≥13.2 Gy).

Rescue with peripheral blood stem cells may increase the risk for MDS/AML compared with bone marrow grafts. Data on 467 French patients who underwent autologous transplantation for HL were matched with data from 1,179 conventionally treated patients listed in international databases. These data showed 18 secondary cancers, leading to a 5-year cumulative incidence of 8.9%. Risk factors for secondary cancer were age of 40 years or older, peripheral blood used as a source of stem cells, and treatment for relapsed disease. Solid tumors were more frequent in patients who underwent transplantation, although the incidence of MDS and AML was similar in the 2 groups.

**Cardiovascular**

HL survivors exposed to doxorubicin and thoracic radiotherapy are at risk for long-term cardiac toxicity, which can increase non-relapse-related mortality. Data from the pediatric HL survivor cohorts in the United States and Nordic countries show overall standardized mortality ratios (SMR) of 10.8, with SMRs for cardiac mortality ranging from 5.8 to 8.2. In 2 U.S. studies in adult HL patients, coronary vascular disease (CVD) accounted for 16% and 13.7% of deaths, respectively. Other data from the Netherlands show an SMR among adults of 6.8 for death from HL and 6.3 from CVD. For patients younger than 21 years at diagnosis, the SMR for CVD was 13.6.

The risks to the heart are related to: individual cumulative anthracycline dose; the total and fraction
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Anthracycline-related cardiomyopathy is associated with female gender, cumulative doses greater than 200 to 300 mg/m², younger age at exposure, and increased time from exposure. Cardiac abnormalities related to doxorubicin exposure may not manifest for many years. The Institut Gustave Roussy recently evaluated cardiac abnormalities in 229 15-or-more-year survivors of childhood cancer who were treated with doxorubicin at a mean dose of 344 mg/m² (range, 40–600 mg/m²) between 1968 and 1982. Eighty-nine (39%) patients experienced significant cardiac disease with a fractional shortening less than 25%, ejection fraction less than 50%, end-systolic wall stress more than 100 g/cm², or clinical heart failure, although 65 of them were asymptomatic. Risk increased with increasing anthracycline dose, but neither age at treatment nor gender influenced risk. Radiotherapy exposure increased risk fourfold (95% CI; 1.0–17.5), as did increased time from treatment.

In a 2004 review on cardiotoxicity in childhood cancer, patients who underwent treatment with doses more than 300 mg/m² experienced dose-responses of 15.5% to 27.8% for subclinical cardiotoxicity and 19% to 52% for abnormal afterload; those who underwent treatment with lower doses experienced dose-responses of 0% to 15.2% for abnormal left ventricular function. A similar study in adult lymphoma survivors who underwent treatment with a mean cumulative dose of 300 mg/m² showed a 20.5% incidence of late subclinical cardiomyopathy.

Pulmonary

Pulmonary fibrotic disease occurs as a late complication after radiation therapy. Acute pneumonitis, manifested by fever, congestion, cough, and dyspnea, can occur after radiotherapy alone at doses of more than 40 Gy administered to focal lung volumes, or after lower doses (15–20 Gy) when combined with chemotherapy administered to generous or whole lung volumes. Lung compromise is a function of radiation dose and volume as well as the overall use of bleomycin. Bleomycin-associated pulmonary fibrosis with decreased diffusion capacity is most commonly seen after doses more than 200 to 400 U/m². At lower doses, significant pulmonary dysfunction is uncommon.

Other chemotherapy agents used in HL, particularly in the relapse setting, including cyclophosphamide, lomustine, carmustine, busulfan, and cytarabine, can have pulmonary effects. Concurrent use of radiation and pulmonary-toxic chemotherapy may be problematic. However, overall, the clinical burden of pulmonary compromise, acute or chronic, seems small, particularly in the modern era of chemotherapy.

A prospective study from Stanford University of pulmonary function in 145 teenagers and adults who underwent treatment from 1980 to 1990 revealed that only 32% of patients treated with mediastinal radiotherapy alone, 37% treated with mediastinal radiotherapy and bleomycin, and 19% treated with bleomycin without mediastinal radiotherapy had forced vital capacity less than 80%, and only 7% had carbon monoxide diffusing capacity less than 70%. Mediastinal radiotherapy was the only therapeutic factor that increased risk. No patients had significant clinical symptomatology to warrant hospitalization.

The use of more tailored radiotherapy fields may further decrease the risk for pulmonary injury.

In a recent retrospective review by the Mayo Clinic, bleomycin-related pulmonary toxicity (BPT) was seen in 25 (18%) of 141 patients treated with bleomycin-containing regimens for HL between 1986 and 2003. More striking was that 6 of these 25 patients (24%) died as a result of BPT. The median 5-year overall survival was 63% in patients with BPT compared with 90% in those without BPT.

Endocrine

Thyroid Gland

Thyroid dysfunction, manifested by primary hypothyroidism, hyperthyroidism, goiter, or nodules, may be seen after radiation therapy to the neck for HL. The likelihood of thyroid dysfunction varies with the dose of radiation and length of follow-up, with the primary manifestation being hypothyroidism after radiotherapy, where the risk is greatest, with doses greater than 30 Gy. The detection depends on the biochemical criteria used to make the diagnosis. In a study of 1,677 children and adults who underwent radiation therapy between 1961 and 1989, the actuarial risk at 26 years for overt or subclinical hypothyroidism was 47%, with a peak incidence at 2 to 3 years after treatment. In a study of patients who underwent treatment between 1962 and 1979, hypothyroidism occurred in 4 of 24 of those who received mantle doses of less than 26 Gy,
but in 74 of 95 of those who received doses of more than 26 Gy. The peak incidence occurred 3 to 5 years after treatment, with a median of 4.6 years. Among 1,791 childhood HL survivors followed up in the Childhood Cancer Survivor Study, 34% reported that they had been diagnosed with at least 1 thyroid abnormality.

For hypothyroidism, a clear dose–response with a 20-year risk of 20% occurred for those who had received less than 35 Gy to the thyroid gland, 30% for those who received 35 to 44.9 Gy, and 50% for those who received more than 45 Gy. Compared with the general age-matched population, HL survivors had a relative risk of 17.1 for hypothyroidism, 8 for hyperthyroidism, and 27 for thyroid nodules. The risk for hypo- or hyperthyroidism increased in the first 3 to 5 years after diagnosis, whereas that for nodules increased 10 and more years after diagnosis. Women were at increased risk for hypothyroidism and thyroid nodules. Although the risk of hyper- and hypothyroidism has been commonly reported at a median of 3 to 5 years after diagnosis, the risk period continues with ongoing follow-up. Thus, long-term monitoring is important.

Reproductive Endocrine

Male Gonadal Function

Spermatogenesis is highly sensitive to cyclophosphamide, procarbazine, and mechlorethamine (nitrogen mustard) used in HL regimens MOPP and COPP (combined with vincristine and prednisone). Therefore, infertility is a common complication for patients after undergoing regimens containing these agents, with azoospermia rates of up to 86%. Reduction in total doses of alkylating-agent therapy in multiagent protocols resulted in less male infertility, as evidenced by the use of doxorubicin, bleomycin, vinblastine, and dacarbazone (ABVD) initially in combination with MOPP or COPP, and now used commonly as sole chemotherapy. Review of the available studies suggests that men who undergo treatment with less than 4 g/m² of cyclophosphamide, without testicular radiation or any other alkylating agent, will probably remain fertile, whereas those who undergo treatment with cumulative doses greater than 9 g/m² will not.

The degree and permanency of radiotherapy-induced damage to the male reproductive system depend on dose, field, and schedule. The greatest shielding to the testes is afforded by using a frog-leg position with an individually fitted shield, which reduces scatter to approximately 0.75% of the pelvic lymph node dose. The germinal epithelium is damaged by much lower doses (< 1 Gy) of radiotherapy than are Leydig cells (20–30 Gy). Doses less than 30 Gy are unlikely to affect endocrine function, and boys can progress through puberty normally. Although temporary oligospermia can occur after these low radiation doses, permanent azoospermia results from doses of more than 3 to 4 Gy. The potential for spermatogenesis to return in the intermediate dose-range of 1 to 3 Gy is variable.

Female Gonadal Function

Risk of menstrual irregularity, ovarian failure, and infertility increases with age at treatment. Among women who undergo treatment with cyclophosphamide and other alkylating agents than in adolescents, with prepubertal females tolerating cumulative doses as high as 25 g/m². This is illustrated in cohorts of both adult and pediatric survivors of HL. In a study of childhood cancer survivors who underwent treatment between 1945 and 1975, the relative fertility of married survivors of childhood HL was 0.77 (95% CI, 0.64–0.92) compared with sibling controls. The relative risk for premature ovarian failure was 3.35 between 21 and 30 years of age and 1.27 between 31 and 40 years of age, compared with the sibling controls. Relative risk between 21 and 30 years of age rose to 9.6 for those who underwent abdominopelvic radiotherapy and alkylating agents. In another study of 719 survivors treated between 1964 and 1988, consisting of 29% lymphoma survivors, a 15.5% failure to conceive occurred. Increasing doses of abdominopelvic radiotherapy and alkylating agents resulted in increased premature ovarian failure and a fertility deficit in the entire cohort. In pediatric patients, substituting cyclophosphamide for mechlorethamine seems to have significantly reduced the risk for ovarian dysfunction, which is then further decreased by reduction in total dose of both agents. In HL regimens that include adult women, risk is also related to the dose of alkylating agents. In the Stanford V protocol designed to reduce alkylating-agent exposure, 2 of 55 women underwent hormone replacement therapy; 43 (78.2%) experienced regular menses; 10 (18.2%)
experienced irregular menses; and 24 conceptions occurred among 19 women.71 The German Hodgkin’s Lymphoma Study Group determined menstrual status for 405 women treated with 1 of 3 regimens from 1994 to 1998. In this cohort, 19.3% had amenorrhea, 38% experienced regular menses, and 42.7% either were of indeterminate status because of oral contraceptive use or had irregular menses. Multivariate analysis showed risk for amenorrhea to be higher in women undergoing 8 cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) than in those receiving ABVD, COPP/ABVD (cyclophosphamide, vincristine, procarbazine, and prednisone alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine), or standard-dose BEACOPP. Other factors that increased risk were advanced-stage HL, age older than 30 years at treatment, and lack of oral contraceptive use during chemotherapy.74 Radiotherapy effects must be considered for female patients also. Blocking is important when pelvic fields are included. Although scattered dose to the ovaries is inevitable, medial or lateral transposition of the ovaries (oophoropexy) results in doses of 8% to 10% and 4% to 5%, respectively, of the pelvic dose.73,76

Reproductive Issues for Both Sexes

Progress in reproductive endocrinology has resulted in the availability of several options for preserving or permitting fertility.65,66 For men, cryopreservation of spermatozoa before treatment is an effective method of circumventing the sterilizing effect of therapy. Although pretreatment semen quality in patients with cancer may be less than that in healthy donors, the decline in semen quality and effect of cryodamage to spermatozoa from patients with cancer is similar to that of normal donors.77–80 For those unable to bank sperm, newer technologies such as testis sperm extraction may be an option, as shown for male survivors of germ-cell tumors who had post-chemotherapy nonobstructive azoospermia. Further micromanipulative technologic advances, such as intracytoplasmic sperm injection, may permit successful fertilization with surgically extracted or even poor-quality cryopreserved spermatozoa.81,82

In pre- and postpubertal women, cryopreservation of ovarian cortical tissue or enzymatically extracted follicles and in vitro maturation of prenatal follicles are of potential clinical use. In vitro fertilization and subsequent embryo cryopreservation have also been successful.83–85 However, these approaches harbor the risk that malignant cells will be present in the specimen and reintroduced in the patient at a later date.84,85 Ethical issues regarding risk and benefit, consent and consent, and disposition of gametes have not yet been resolved.86

As use of assisted fertility techniques increases, the risk for congenital anomalies will need to be followed closely because increased anomalies in offspring born by in vitro fertilization or intracytoplasmic sperm injection have been reported.87–90

Spleen

Splenectomy increases risk for life-threatening invasive bacterial infection and can lead to altered immune function.92 With practices changing to omit staging laparotomy from the treatment of patients with HL, the previously described long-term complications, both related to surgery and altered immune function, should no longer be an issue for most survivors. However, patients may also be rendered asplenic by radiation therapy to the spleen in doses of more than 30 to 40 Gy. Low-dose involved-field radiation (21 Gy) given with multiagent chemotherapy does not seem to adversely affect splenic function.93

Psychosocial and Central Nervous System

Survivors of HL are at risk for adverse psychologic outcomes. In the Childhood Cancer Survivor Study, 5.4% of 1,843 HL survivors reported symptoms of depression and 15% reported somatic distress higher than that for other malignancies or from a sibling cohort. Female gender, lower household income, less than a high school education, and lack of current employment increased risk for depression and somatic distress symptoms, with older age also increasing risk for somatic distress.94 Results from the Italian Multicentric Study on Long-Term Survivors of Childhood Cancer support the finding of psychologic distress. A cohort of 337 survivors of leukemia and lymphoma showed increased self-reported feelings of anxiety, depression, panic attacks, and fear of recurrence compared with siblings, and these differences were more marked when compared with
friends and other relatives. Similar findings of depressed mood and somatic distress are reported in adult survivors, for whom issues of chronic fatigue, cognitive impairment, and sexual dysfunction also are prevalent.

No CNS-directed therapy is available for HL, and CNS abnormalities have not been well studied. However, the Childhood Cancer Survivor Study found HL survivors to have an increased need for special education compared with siblings (OR = 4.4; 95% CI, 2.6–7.2), consistent with adult data reporting cognitive impairment. Data from that study also indicate that HL survivors are at increased risk for developing stroke (RR = 4.3; 95% CI, 2.0–9.3). All 24 survivors with stroke received mantle radiotherapy with a median dose of 40 Gy. However, this complication may represent carotid artery or cardiovascular disease related to radiotherapy damage to the intima of the vessels. With the reduced doses and volumes delivered to the mantle in contemporary therapy, whether this will remain an ongoing risk for HL survivors is not clear.

**Future Directions**

Although associations between certain therapeutic exposures and adverse physiologic outcomes of HL are well known, the mechanisms underlying many of these outcomes remain largely unknown. Considerable variability exists in the proportion of survivors that develops treatment-related toxicities despite common treatment exposures. Experts are unsure whether these events are stochastic or if host-related factors, such as inherited differences in drug metabolism and activation, radiation sensitivity, and DNA repair, influence the risk for long-term toxicity.

Whether these study results should affect clinical practice should also be considered. For example, a retrospective analysis on a case of secondary leukemia after neuroblastoma showed the leukemogenic translocation involving the MLL gene at 11q23 before the onset of secondary leukemia. The question arises whether patients receiving topoisomerase II inhibitors or alkylating agents (for HL or other malignancies) should undergo routine bone marrow screening to predict increased risk for secondary leukemia. More research is needed to balance risk and benefit.

Although experts have examined how morbidity and premature mortality are affected by treatment exposures, they have not explored their relationship to other factors, such as environmental exposures that are etiologically related to the major problems in an aging population. Determining these relationships requires creative research efforts. New patterns of late morbidity and mortality may emerge as survivors age. Continued study will identify such patterns and help clinicians develop interventions for treatment and prevention.

Although much has been published on adverse long-term sequelae in survivors of HL, the true incidence and prevalence remain unknown. The relevant denominator in these studies is never all patients at risk, and selection bias occurs even in the best studies. However, these studies support monitoring survivors for these adverse sequelae. Guidelines for scoring and monitoring late effects have been published by pediatric and radiation oncology groups, and should assist clinicians in the appropriate follow-up of these survivors. However, because some late effects are relatively rare and testing the guidelines in survivor populations is difficult, these guidelines are not always consistent, and recommendations have differing levels of evidence-based validity.

This is particularly problematic when therapy changes over successive treatment eras. Regardless of inconsistencies, however, certain monitoring and risk-reduction strategies are clear. Survivors of HL should, at minimum, undergo routine cancer screening recommended for the general population. Those at higher risk should undergo additional screening, usually starting younger than recommended for the general population. Survivors of HL should undergo a general medical evaluation at least annually and should be cautioned against health behaviors that could increase risk of adverse long-term effects. For example, smoking can increase risk of cardiovascular or pulmonary disease and of secondary breast cancer; excessive sun exposure can increase the risk of skin cancer; and high fat diet, sedentary lifestyle, and obesity can increase the risk of cardiovascular disease. Further research is needed to quantify adverse long-term outcomes and develop risk-reduction strategies. Extrapolating from the general population or other cancers may be valuable.

In conclusion, survivors of HL are at increased risk for toxicity of a number of organ systems, second malignancies, and psychosocial complications. However, the success in curing patients with HL should not be overshadowed by the risk of long-term adverse events. Instead, we should learn from these studies.
and try to design balanced therapies. In addition, systematic follow up and ongoing research should focus on this growing cohort of survivors, for whom the quality of life is of paramount importance.

References


Lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives.  


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