Long-term Toxicity of Chemotherapy and Radiotherapy in Lymphoma Survivors: Optimizing Treatment for Individual Patients

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Abstract: Lymphoma treatment has evolved to reflect the fact that even when cure is achieved, significant chronic or late-onset toxicity can vitiate long-term patient outcomes. Previously, the sole focus of treatment was on maximizing cure rates. Now, the emphasis is on titrating treatment intensity to retain or improve cure rates while limiting treatment-associated late effects. To accomplish this on an individual basis remains clinically challenging. Most of the agents used in the treatment of Hodgkin and non-Hodgkin lymphoma have the potential to produce late-manifesting toxicities such as cardiac dysfunction, second malignancy, and infertility. This review outlines some of the evidence regarding late effects of chemotherapy and radiation for lymphoma, with emphasis on how understanding individual patient characteristics can affect the potential late toxicity of different treatment options.

Introduction

Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program show that the US 5-year relative survival rate is 88.3% for patients with Hodgkin lymphoma (HL) and 70.3% for those with non-Hodgkin lymphoma (NHL).[1] These rates have improved by 15% to 25% over the last 25 years. Consequently, the risk of chronic or late-onset toxicity has emerged as an important consideration in the management of lymphoma patients. The purpose of this work is to review the current understanding of the long-term risks associated with lymphoma treatment, and to illustrate selected clinical circumstances in which consideration of late toxicity supports the individualization of treatment rather than the formulaic application of uniform treatment protocols.

To illustrate how clinicians must balance the goals of cure and long-term health, this review presents 3 cases and relates them to the issues of cardiac toxicity, second malignancy, and fertility.

Overview of Cases

Case 1

Case 1 is a 37-year-old woman who presents with bulky stage IIA primary mediastinal B-cell lymphoma. She is concerned about the increase in risk of breast cancer from radiotherapy (RT). She and

her husband were planning to start trying to have children before she received her diagnosis.

Cases 2 and 3

Case 2 is an 18-year-old young woman who presents with bulky stage IIA HL (Figure 1A). Case 3 is a 32-year-old man who presents with stage IIB HL with supraclavicular nodal bulk, nonbulky anterior mediastinal disease (Figure 1B), and an elevated erythrocyte sedimentation rate. Both patients fall into the early unfavorable risk category by German Hodgkin Study Group (GHSG) criteria, and the woman is considered intermediate risk by Children's Oncology Group criteria.

Cardiac Toxicity

Both RT and doxorubicin can lead to cardiac toxicity. The risk of these may be affected by a variety of modifying factors.

Radiation Therapy

RT in young patients produces late-onset intimal thickening in the coronary arteries, and microvascular damage that causes reduced myocardial perfusion. Mantle field RT at prescribed doses of 35 to 45 Gy has been shown to increase the risk of multiple forms of late-onset cardiac toxicity.[2] Coronary artery disease accounts for 40% to 50% of adverse cardiac events among long-term HL survivors. Valvular disease is less common, typically occurs more than 10 years after treatment, and is associated with high radiation doses (>30 Gy) or young age at treatment. The standardized incidence ratio (SIR) of significant cardiac morbidity is elevated approximately 2- to 4-fold following mantle field RT, and the cumulative risks of significant heart disease among survivors of adult HL are approximately 5% to 10% at 15 years, and 35% at 30 years.[3,4]

Radiation-related late cardiac effects are dose-related. Hancock and colleagues, for example, found that the increased risk of cardiac death was restricted to those who received prescribed doses greater than 30 Gy to the mediastinum, whereas no significant increase in the risk of cardiac death was found among patients who received lower doses.[5] Among survivors of childhood HL, 2 studies have found that cardiac-related deaths occurred among patients who received mediastinal doses greater than 30 Gy.[5,6] In one of the few studies to estimate the actual cardiac dose (rather than the prescribed dose to the mediastinal lymph nodes), Mulrooney and coinvestigators evaluated the cardiac outcomes of 14,358 5-year survivors of pediatric cancers with a variety of primary diagnoses who were registered in the Childhood Cancer Survivor Study. Mean heart doses greater than 15 Gy were associated with significantly increased risks of myocardial infarction (MI), heart failure (HF), pericarditis, and valvular disease, whereas mean doses less than 15 Gy were not associated with a significant increase in any of these adverse outcomes.[7]

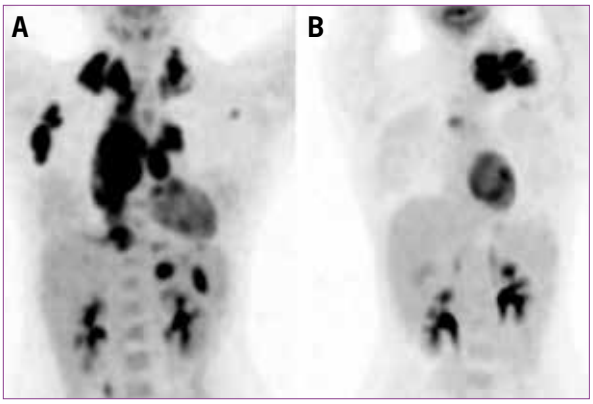

Figure 1. Staging ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography image of 2 patients with early stage unfavorable (intermediate-risk) Hodgkin lymphoma. **A** is from a young woman with bulky stage IIA Hodgkin lymphoma, and **B** is from a man with stage IIB Hodgkin lymphoma and peripheral bulk. The risks associated with radiotherapy are substantially different for these patients, despite their being in the same prognostic category.

This is relevant to the contemporary treatment of lymphoma insofar as mediastinal involved-site RT (ISRT) is emerging as a recommended approach for delivering RT to patients with lymphoma.[8,9] ISRT involves treatment of involved nodal regions only—based on available computed tomography and positron emission tomography imaging—with no prophylactic nodal treatment to uninvolved sites. This approach significantly reduces the mean radiation dose to the heart compared with mantle field RT. Maraldo and colleagues, for example, evaluated cardiac dosimetry in 29 adults with supradiaphragmatic stage I/II HL. They reported that the mean dose to the heart was 7.7 Gy with contemporary RT fields (prescribed dose, 30-36 Gy) vs 27.5 Gy for mantle RT fields (P<.001; prescribed dose, 36 Gy). Notably, the cardiac dose associated with contemporary treatment was highly dependent on the anatomic distribution of disease, creating a significant variation in heart dose among individuals with modern RT (range, 0-22.4 Gy).[10] In addition to using smaller RT target volumes, the use of modern intensity-modulated RT using nonopposed oblique beams, along with motion-management techniques such as moderate deep inspiration breath hold during RT, have been shown to allow significant reductions in the cardiac dose for patients treated for mediastinal lymphoma.[11,12]

Given the available evidence, it should be a goal to keep the mean heart dose to less than 15 Gy among those receiving mediastinal RT. This should be achievable in most early-stage cases prescribed 30-Gy ISRT.

The option to prescribe 20 Gy to very favorable risk cases after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) should reduce the heart dose (and anthracycline exposure) further.[13] Considering the eligibility criteria of the GHSG HD10,[13] most patients eligible for 2 cycles of ABVD and 20-Gy involved-field RT (IFRT) or ISRT would receive limited cardiotoxic exposure and likely would increase the 20-year long-term cumulative incidence of heart disease by less than 5% compared with the age- and sex-matched general population, although the effects of contemporary treatment as patients age and accumulate additional cardiac risk factors remain unknown.

Doxorubicin

The anthracycline agent doxorubicin is directly toxic to the myocardium through a variety of mechanisms, including free radical–mediated oxidative damage and induction of cellular apoptosis. The incidence of acute HF has been estimated at 3% to 5% with a cumulative dosage of 40 mg/m^2, and at 7.5% to 26% with a dosage of 550 mg/m^2.[14] These are significantly higher dosages than the 300 mg/m^2 typically received by patients treated with 6 cycles of ABVD or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

The cardiac effects of moderate-dose doxorubicin, given as part of ABVD or R-CHOP to young adults, are less clear. With a short median follow-up of 2.7 years, Swerdlow and colleagues found that treatment with doxorubicin without supradiaphragmatic RT was associated with a significantly increased risk of fatal MI (standardized mortality ratio, 3.2; P<.001), and ABVD was associated with a 7.7-fold increased risk (P=.01).[15] In contrast, 2 other studies of HL survivors did not find a significantly increased rate of late cardiac morbidity among young adults initially treated with chemotherapy alone, although the number of patients treated with ABVD in these series was small.[3,16] A recent study of 53 patients treated with 50 to 375 mg/m^2 of doxorubicin-equivalent chemotherapy for a variety of different cancers (average age at treatment, 50 years) found significant deterioration in several echocardiographic measures of ventricular function and quality of life within 6 months of treatment.[17] Limat and coinvestigators evaluated clinically significant cardiac events—defined as a decline in resting left ventricular ejection fraction (LVEF) of 20% or greater from baseline, absolute LVEF of less than 50%, or clinical evidence of HF—among 180 patients treated with CHOP chemotherapy (median doxorubicin dose, 348 mg/m^2; range, 200-430 mg/m^2). For the overall cohort, the 5-year cumulative risks of significant cardiac events and clinical HF were 19% and 10%, respectively. In multivariate analyses, age less than 60 years at treatment and the use of dexrazoxane were associated with significant reductions in the risk of cardiac toxicity (hazard ratio [HR], 0.4 and 0.1, respectively). Notably, the 5-year cumulative risk of cardiac event decreased from 29% to 8% (P=.006) during the periods before and after the introduction of cardioprotection.[18]

In most studies, the combined use of doxorubicin and mantle field RT has been associated with a greater risk of late cardiac toxicity than either treatment given alone. Myrehaug and colleagues reported that, for men treated for HL at age 40 years, the estimated 15-year rate of cardiac-related hospitalization was 9.8% (SIR, 1.92) following mantle RT (median dose, 35 Gy), and 16.5% following combined doxorubicin with mediastinal RT (SIR, 2.80).[16] And in a study of 1474 HL survivors, Aleman and colleagues found that the addition of anthracyclines to mediastinal RT significantly increased the risk of HF (relative risk [RR], 2.81) and valvular disease (RR, 2.10) vs mediastinal RT alone, but did not increase the risk of MI.[3]

Modifying Factors

Age is a significant modifier of anthracycline-related cardiotoxicity. Among survivors of childhood lymphoma, unrecognized myocardial damage caused in early life may manifest itself years later as a reduction in myocardial wall thickness and ventricular dilatation. A recent study of 125 pediatric lymphoma survivors with a median follow-up of 20.4 years reported that 50% had echocardiographic evidence of abnormal left ventricular function, valve dysfunction, or both.[19] Other investigators have also reported echocardiographic abnormalities in more than 30% of childhood cancer survivors 10 to 30 years after treatment.[7]

The Childhood Cancer Survivor Study reported increased risks of HF among children treated with anthracyclines compared with individuals who had not been exposed (HR, 2.4 for <250 mg/m^2 doxorubicin equivalent and 5.2 for ≥250 mg/m^2) compared with individuals who had not been exposed to anthracyclines. Patients receiving 250 mg/m^2 or greater had a 25-year risk of HF of approximately 5%, with no apparent plateau in risk with longer follow-up. At the other end of the age spectrum, elderly patients with diffuse large B-cell lymphoma (DLBCL) also have been shown to experience an elevated risk of clinically apparent HF after doxorubicin-based treatment. As noted above, Limat and coinvestigators found that age greater than 60 years was a significant risk factor for the development of HF with CHOP chemotherapy.[18] Hershman and colleagues analyzed data on 6388 patients of at least 65 years of age from the SEER cancer registry.[20] The 8-year rate of HF was 26% among those receiving doxorubicin vs 21% among those treated without doxorubicin (HR, 1.29; 95% CI, 1.02-1.62). An increase in the number

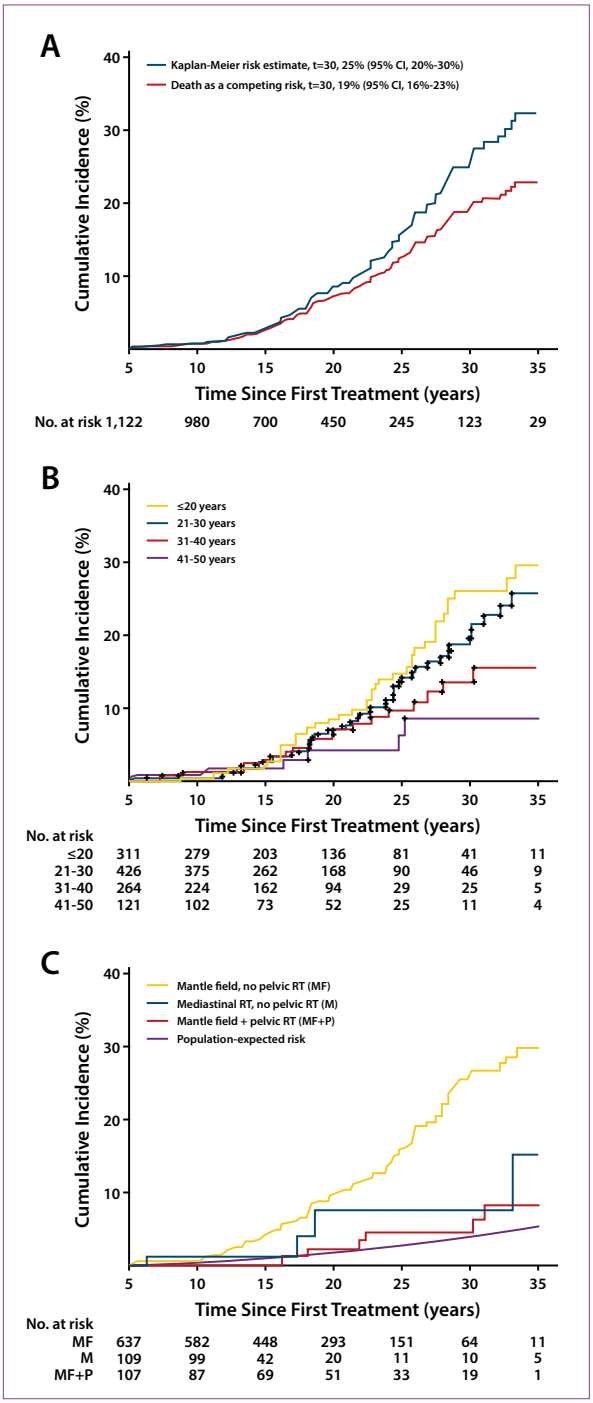

Figure 2. The cumulative incidence of breast cancer after Hodgkin lymphoma. **A,** Cumulative risk and incidence of breast cancer (invasive plus ductal carcinoma in situ). **B,** Cumulative incidence of breast cancer according to age at first treatment. **C,** Cumulative incidence of breast cancer according to radiation fields and population-expected risk.

M, mediastinal; MF, mantle field; No., number; P, pelvic; RT, radiotherapy.

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of cycles of doxorubicin-containing chemotherapy was significantly associated with increasing risk of HF. Similarly, a recently reported clinical trial designed to evaluate cardiac toxicity associated with 2 different chemotherapy regimens for DLBCL (median age at treatment, 68 years) found that 17% of patients developed reductions in LVEF greater than 20% from baseline, and 6% developed clinically apparent HF after 6 to 8 cycles of R-CHOP.[21]

The effects of age on the toxicity of RT are less clear, but most studies show that older age is associated with greater increase in the absolute excess risk of heart disease following RT for HL.[3,15]

Females treated in childhood are at greater risk of developing doxorubicin-induced ventricular dysfunction than are males.[7] In contrast, most studies of adult lymphoma survivors find a greater risk of cardiac complications (primarily coronary artery disease) among males following mediastinal RT, although there does not appear to be a synergistic interaction between sex and the impact of radiation on the risk of heart disease.[3,4,16]

The presence of 1 or more conventional cardiac risk factors (diabetes, elevated cholesterol, smoking, and hypertension) has a significant effect on the incidence of heart disease among both HL survivors and older patients with DLBCL, although it is not clear if these risk factors produce supraadditive enhancement of treatment toxicity. Aleman and coinvestigators found that conventional risk factors significantly increased the risk of cardiac morbidity among HL survivors, although there was not a statistically significant interaction between cardiac risk factors and HL treatment on the risk of adverse cardiac events.[3] In contrast, Glanzmann and colleagues evaluated 352 patients following mediastinal RT and found that the risk of cardiac events was significantly increased only among those with cardiac risk factors.[22] Other investigators also have found that patients who developed coronary artery disease after mediastinal RT typically have at least 1 conventional risk factor.[23]

One study of 1096 HL patients found that preexisting heart disease was the strongest predictor of cardiac hospitalization after treatment (HR, 3.98 compared with survivors without preexisting heart disease). Furthermore, prior heart disease significantly modified the effect of mediastinal RT on subsequent cardiac risk. For patients with pretreatment heart disease, mediastinal RT plus doxorubicin-based chemotherapy was associated with a 10-year incidence of cardiac hospitalization that was more than 20% higher than treatment without RT.[24] The SEER study of elderly DLBCL patients also found that diabetes, hypertension, and preexisting heart disease significantly increased the risk of HF following anthracycline chemotherapy, and that hypertension had a statistically significant synergistic interaction with doxorubicin exposure that further increased the HF risk (HR, 1.8; P=.01).[20]

Second Malignancy

An increased risk of second cancers following treatment for HL has been recognized for more than 2 decades, and remains a source of clinical concern. More recently, survivors of NHL also have been shown to be at increased risk for leukemia, colorectal cancer, lung cancer, and other solid tumors.[25] These findings potentially are taking on greater significance as primary disease control continues to improve for NHL patients.

Breast Cancer

Mantle RT, which historically delivered doses of 35 to 45 Gy, increases the RR of breast cancer in young female HL survivors 2- to 20-fold, largely depending on age at exposure. The cumulative incidence of breast cancer for adolescents and young adults who received this treatment is approximately 15% to 20% at 30 years after treatment.[6,26,27] In both children and adults, studies have demonstrated an increasing risk of breast cancer with increasing radiation dose, up to approximately 40 Gy.[28-30] This is significant insofar as most published studies of second cancer after RT primarily include patients treated with mantle fields, whereas smaller IFRT, in which prophylactic nodal radiation is typically limited to 1 echelon of adjacent lymph nodes, has been the standard approach for approximately 15 to 20 years. Typically, an IFRT treatment would, for example, not irradiate uninvolved axillary nodes, a maneuver that reduces the breast radiation dose by approximately 65% for females with mediastinal disease.[31] Early indications from long-term follow-up studies indicate that this reduction in breast radiation dose produces a corresponding reduction in breast cancer risk. A study of 1122 female HL survivors found that 36- to 44-Gy mantle field irradiation was associated with a 2.7-fold (95% CI, 1.1-6.9) increased risk of breast cancer compared with radiation to the mediastinum alone (Figure 2C).[32] Similarly, Franklin and colleagues reported a significantly higher risk of breast cancer (odds ratio [OR], 3.25) with extended-field RT compared with IFRT.[33]

As noted above, ISRT is emerging as a recommended approach to delivering RT to patients with lymphoma. Dosimetry studies suggest that this will, on average, produce a roughly 33% to 45% reduction in breast exposure compared with IFRT.[34,35] One feature of ISRT, however, is its dependence on the anatomic distribution of disease, so that significant variation in normal tissue dose among individuals—and the associated potential late toxicity—is more important to consider than it has been historically.

Lung Cancer

In studies of outdated HL treatments, lung cancer risk is often increased among survivors.[36,37] The RR is increased most among young patients, with a recent meta-analysis reporting an 8.76-fold increase in the risk of lung cancer among those receiving mantle RT at ages 15 to 24 years, in contrast to a 2.88-fold increase among those aged 55 years or older.[38] However, it is notable that the absolute excess risk—the more clinically important measure—is small in the first 20 years after exposure, particularly among those treated before age 20 years. In this case, the 20-year cumulative incidence is less than 5% (eg, ≤0.2 per 10,000 person-years).[39,40]

Similar to breast cancer, the risk of lung cancer also rises with increased radiation dose up to 40 Gy and with an increased volume of lung irradiated,[41,42] suggesting that contemporary ISRT fields should be associated with lesser risks than historic mantle treatment.

The alkylating agents mechlorethamine and procarbazine have been associated with significant dose-dependent elevations in lung cancer risk (RR, 1.5-6.1).[41,43] For example, a cohort study of 5519 patients showed a significantly elevated risk of lung cancer (SIR, 3.3) following chemotherapy alone (mostly alkylator-based), which was similar to the risk following RT (SIR, 2.9).[40] The reduction or elimination of these agents from most contemporary chemotherapy regimens should significantly reduce the risk of chemotherapy-associated lung cancer for most HL patients.

Mudie and colleagues reported outcomes of the British National Lymphoma Investigation study of 2465 patients treated for NHL before age 60 years (average age at first treatment, 46.5 years), including 1219 patients receiving CHOP, and found that the risk of lung cancer was significantly raised in the CHOP subcohort (RR, 2.1), as was the risk of colorectal cancer (RR, 2.4).[44] The authors suggested that further study was warranted to determine whether cyclophosphamide exposure in older patients was convincingly associated with an increasing second cancer risk.

Leukemia

Historically, mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) chemotherapy has been associated with 20- to 50-fold increased RR for acute myeloid leukemia (AML), with a 5- to 15-year cumulative incidence of 5% to 10%.[45,46]

The replacement of alkylator-based chemotherapy with ABVD chemotherapy has significantly reduced the risk of treatment-associated AML. A large international cohort study of patients treated from 1970 through 2001 showed that the excess absolute risk of AML declined significantly after 1984, from 7.0 to 4.2 per 10,000 persons per year, likely owing to changes in preferred chemotherapy regimens.[47] Clinical studies of patients treated with ABVD typically have reported a 5- to 15-year cumulative risk of AML of less than 2%.[48]

Topoisomerase II inhibitors such as etoposide have also been associated with an elevated risk for AML.[49,50] This is of concern insofar as some contemporary chemotherapy regimens such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP); vincristine, etoposide, prednisolone, and doxorubicin (OEPA); and CHOP plus etoposide (CHOEP) potentially could be more leukemogenic than alternative effective regimens. A recent report of GHSG trials found that the 6-year cumulative incidence of AML or myelodysplastic syndrome (MDS) was 1.7% for patients who had 4 or more cycles of escalated BEACOPP (escBEACOPP), vs 0.3% and 0.7% (P<.0001) for those treated without escBEACOPP chemotherapy or with fewer than 4 cycles of escBEACOPP, respectively.[51] The addition of etoposide to R-CHOP for DLBCL or in OEPA for pediatric HL, however, does not appear to be associated with an increase in the risk of treatment-related AML compared with their non–etoposide-containing counterparts.

Most studies have reported a noticeably higher risk of leukemia following treatment for NHL than for HL. In the British National Lymphoma Investigation study of NHL, the RR of leukemia following CHOP chemotherapy was 14.2 (95% CI, 6.8-26.2).[44] Tam and coinvestigators found that among 137 patients treated with fludarabine-containing combination regimens for indolent lymphomas, the cumulative incidence of MDS at 40 months was estimated to be 6%.[52] In addition, an Italian study of 563 patients with indolent NHL found that fludarabine was associated with an increased risk of second malignancy in multivariate analysis.[53]

The cumulative incidence of AML/MDS after salvage chemotherapy and autologous stem cell transplant (ASCT) is 1% to 14%. Agreement does not exist on the extent to which ASCT itself contributes to this risk, however, because much of this risk may be associated with chemotherapy exposure before transplant.[54] One study compared the risk of AML/MDS between 1530 patients who underwent conventional therapy and 202 HL patients who underwent ASCT.[55] The 15-year cumulative risk of developing AML/MDS was 1.1% for those treated with conventional therapy alone, and 3.6% for those undergoing ASCT (P=.22). In contrast, Moser and colleagues analyzed second cancer risks among 748 patients treated with CHOP or CHOP-like regimens for aggressive-histology B-cell lymphomas, and in multivariable analyses found that receipt of salvage therapy was the only treatment factor significantly associated with an increased risk for second malignancy (HR, 1.75).[56] These 2 study results are not necessarily incompatible, and differences in analytic approaches and the associated differences in P values should not obscure the observation that both studies find a small increase in the risk of AML/MDS after ASCT.

Modifying Factors

Smoking appears to augment the effects of both RT and alkylator chemotherapy on the risk of lung cancer.[57] In 1 large case-control study of HL survivors, only 3.2% (7 of 222) of lung cancers occurred in patients who had never smoked. Smoking was estimated to contribute to 87% of observed lung cancers, whereas 9.6% were attributed to treatment.[43]

Age at treatment has a significant effect on the risk of a second malignancy. One of the best-recognized examples is the increased relative risk of breast cancer following mediastinal RT among young women, which over many years of follow-up translates into a substantially greater excess absolute risk. Females treated before age 20 years have a significantly higher risk than those treated after age 35 years, and those receiving RT after age 40 years typically have a small increase in risk (RR, 1.2-2.5).[37,40,58] This age effect may be in part due to the longer duration of intact ovarian function after RT among younger patients.[32]

Older age is associated with an increased risk of treatment-related AML. The median age of patients with treatment-related AML/MDS in the GHSG protocol, for example, was significantly greater than that in the whole population group (43 vs 34 years).[51]

The risk of a second malignancy after RT is strongly influenced by sex. Young females have a significantly higher risk of radiation-related second malignancies than males. In a study of 930 children treated for HL, the risk of a second malignancy was significantly higher among females (SIR, 19.9) than males (SIR, 8.4), largely owing to the excess risk of breast and thyroid cancer. The 25-year cumulative incidence of second cancers was approximately 30% among females and 14% among males.[59]

Fertility

Fertility is a relatively understudied outcome among lymphoma survivors. Recent work has demonstrated that lymphoma survivors are more likely to be childless than their age- and sex- matched peers, that they do not commonly make use of available fertility preservation strategies, and that they often are uncertain about their fertility after treatment. In addition, they often experience sexual dysfunction after treatment.[60]

It is now well established that alkylating agents and gonadal radiation can produce a significant dose-dependent risk of infertility among lymphoma survivors. Approximately 50% of young women receiving 9 g/m^2 of cyclophosphamide will develop premature ovarian failure (POF), and there is an estimated 11% increase in the risk of POF with each additional 1.4 g/m^2 of procarbazine exposure.[61,62]

RT to pelvic or inguinal lymph nodes can be associated with clinically significant exposure to the ovaries or testes. Bilateral ovarian radiation doses of 2 to 5 Gy will produce POF in approximately 35% of young females and in the majority of women older than 40 years of age, whereas doses greater than 5 Gy will sterilize the large majority of female patients regardless of age.[62] The testes are very sensitive to low doses of radiation, with temporary oligospermia occurring at doses from 0.1 to 0.3 Gy and permanent azoospermia reported with doses greater than 3 Gy.

Contemporary chemotherapy regimens have less impact on fertility than historically used alkylator-based treatment. More than 90% of young women receiving 2 to 4 cycles of ABVD will have resumption of menstrual cycles within 1 year of completing treatment, and women attempting pregnancy after ABVD have success rates equivalent to those of age-matched controls, with approximately 75% to 80% achieving pregnancy.[63,64] Similarly, sperm counts and/or follicle-stimulating hormone levels are normal in 50% to 75% of males following ABVD chemotherapy.[63,65]

CHOP-based chemotherapy also appears to have a limited effect on fertility. Meissner and colleagues reported the reproductive outcomes among 101 patients treated in 2 large trials comparing CHOP-based chemotherapy regimens (median age at treatment, 32 years).[66] Among 36 patients who attempted to reproduce, 26 (72%) were successful without requiring medical intervention. The percentage of childless female survivors was comparable to age- and sex- matched rates from the general population (21.7% vs 20.8%), although the proportion of childless male survivors was somewhat higher than age- and sex-matched rates from the general population (41.8% vs 32.6).[66] These results are consistent with the expectation that the cumulative dosage of 4.5 g/m^2 of cyclophosphamide delivered with 6 cycles of CHOP should have a small impact on the fertility of younger women.

In some circumstances, it can be desirable to employ a dose-intensive chemotherapy regimen in selected patients to improve progression-free survival. Dose-adjusted rituximab, etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (DA-R-EPOCH), for example, has been reported to produce excellent disease control and limit the requirement for mediastinal RT among patients treated in nonrandomized studies for primary mediastinal B-cell lymphoma.[67] A recent survey of 20 female patients treated with 6 to 8 cycles of DA-R-EPOCH found that 14 (70%) developed amenorrhea while on chemotherapy. The majority of patients recovered, however, with 15 patients (75%)—all 35 years of age or younger—reporting menstrual periods following completion of treatment. Six patients (30%) conceived naturally and gave birth to healthy children. Patients treated at age 40 years or older, however, had biochemical profiles indicative of POF.[68]

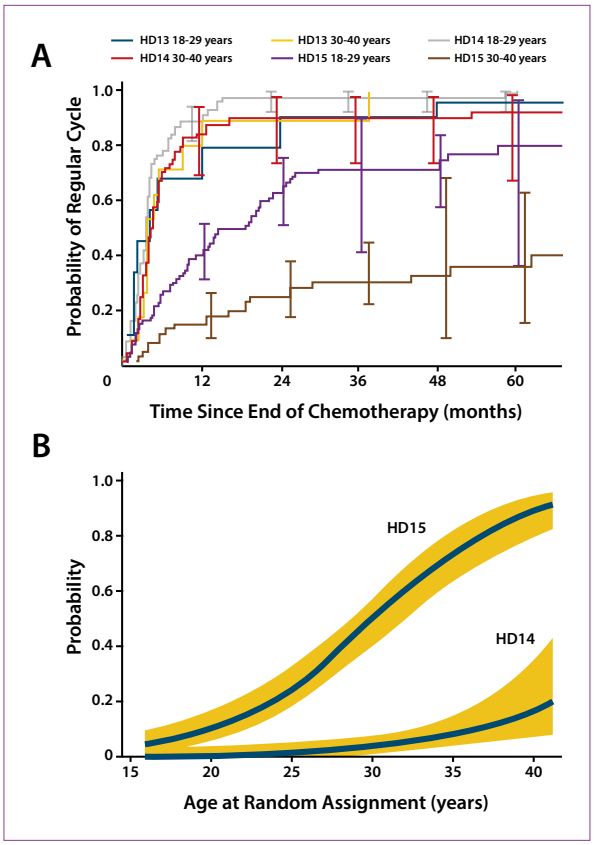

Figure 3. A, Time to regular cycle in the 3 trials and 2 age groups. Generalized Kaplan-Meier estimates shown with 90% CIs for HD14 (ABVD) and HD15 (BEACOPP). **B,** Probability of amenorrhea 4 years after chemotherapy. The significant influence of age at therapy is shown (estimates of logistic regression analyses for HD15 and HD14 at the mean time after chemotherapy, 47 months [with 90% CIs]).

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.

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Similarly, escBEACOPP has been shown to produce better primary disease control than ABVD among high-risk HL patients.[69] Behringer and coinvestigators reported gonadal toxicity among 1323 patients treated on sequential GHSG trials with ABVD and/or escBEACOPP. After 6 to 8 cycles of escBEACOPP, 34% of women treated at age 30 years or older experienced severe menopausal symptoms. More than half of women treated at age 35 years or older had persistent posttreatment amenorrhea, whereas 25% of women aged 25 had this complication (Figure 3). Similarly, more than 80% of males treated with escBEACOPP had inhibin and follicle-stimulating hormone levels after treatment that were consistent with impaired fertility, with better recovery of hormonal indices among younger men.[63]

There are few studies that meaningfully quantify the risk of infertility following salvage therapy with ASCT. Swerdlow and colleagues reported that among 58 women treated with bis-chloroethylnitrosourea (BCNU), etoposide, cytarabine, and melphalan (BEAM) without pelvic RT, 75.3% experienced menopause by age 40 years, although most also had received other alkylating agents.[62] Carter and coinvestigators reported pregnancy outcomes in 619 women and partners of men treated with ASCT (n=241) or allogeneic hematopoietic cell transplantation (n=378) between 21 and 45 years of age, and surviving 2 or more years (median age at transplant, 33.3 years). Thirty-four patients reported 54 pregnancies, which resulted in 46 live births. Older age at hematopoietic cell transplantation (≥30 years; OR, 4.8), female sex (OR, 3.0), and total body irradiation (OR, 3.3) were associated with absence of reported pregnancy.[70] Similarly, Brice and colleagues reported pregnancy rates among 210 women (median age at diagnosis, 27 years; range, 15-40 years) with newly-diagnosed NHL treated with 4 cycles of doxorubicin, cyclophosphamide, vinblastine, and bleomycin (ACVB) followed by cyclophosphamide, BCNU, and etoposide (CBV) and ASCT (total cumulative cyclophosphamide dose, 10.8 g/m^2) or sequential chemotherapy (total cyclophosphamide dose, 7.8 g/m^2). Among 56 women undergoing ASCT, 9 (16%) became pregnant, whereas 5 of 53 (9%) undergoing sequential chemotherapy became pregnant. Notably, all pregnancies occurred among women younger than 29 years at NHL diagnosis.[71] A study of semen analyses among 64 men following bone marrow transplant found azoospermia in 70.3% of survivors. Recovery of spermatogenesis was observed in 90% of patients who received cyclophosphamide, 50% of patients who received cyclophosphamide plus busulphan or thiotepa, and 17% of patients who received cyclophosphamide plus total body irradiation.[72]

Taken together, these results provide some reassurance that dose-dense regimens do not preclude subsequent pregnancy among young survivors, although the extent of associated subfertility and the duration of fertility following treatment remain unknown. It is clear that older age (ie, ≥35 years) is associated with an increased risk for premature menopause following treatment with contemporary dose-intensive regimens.[73]

Resolution of Cases

Case 1

For patients with primary mediastinal lymphoma, appropriate management options include R-CHOP followed by 30- to 40-Gy adjuvant RT, or 6 to 8 cycles of DA-R-EPOCH alone. (Omission of adjuvant RT in patients with a complete response following R-CHOP is the subject of an ongoing randomized trial and is beyond the scope of this paper). Given the patient's age of 37 years, the 30-year breast cancer risk associated with adjuvant mediastinal RT without axillary irradiation is likely 8% to 12%, compared with 3% to 5% in the general population.[32,37,40,74,75] Appropriate screening should limit the probability of the patient dying of breast cancer in the next 30 years to less than 5%. Although her probability of retaining fertility after R-CHOP is not well quantified, early evidence suggest that she is unlikely to remain fertile after 6 to 8 cycles of DA-R-EPOCH. A referral to an appropriate specialist for a discussion regarding oocyte preservation is warranted, but if retention of fertility is a priority for her, R-CHOP is likely the preferred treatment. Notably, if the patient were in her early 20s, the late-effect trade-offs might be better addressed with DA-R-EPOCH and avoidance of RT.

Cases 2 and 3

Although cases 2 and 3 nominally fall in the same prognostic category, their gender, age, and disease distribution create significant differences in their risks of late effects. One reasonable treatment options is chemotherapy using doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) with response-adapted use of 21-Gy RT. This regimen produced a 4-year event-free survival of 85% in the AHOD 0031 study from the Children's Oncology Group, and allowed 45% of patients to be treated without RT.[76] Alternatively, data from the GHSG would support the use of 4 cycles of ABVD with 30-Gy adjuvant RT (5-year freedom from treatment failure [FFTF], 87.7%), or 2 cycles of escBEACOPP and 2 cycles of ABVD followed by 30-Gy RT (5-year FFTF, 95.4%).[69]

It is apparent from the staging imaging that ISRT would irradiate a significantly larger volume of normal tissue in the female patient than in the male. Moreover, for adolescent patients treated with RT, some studies find the cumulative incidence of second cancers to be more than 2-fold greater among females than among males. Treatment using the AHOD 0031 protocol would offer the female patient the best evidence-based opportunity to avoid RT, and a 33% reduction in dose if RT were required owing to slow or incomplete response. The ISRT field for the male patient would not treat the heart, and would be associated with an incidence of a second cancer that was approximately 5% to 10% greater than that of the general population by the age of 60 to 65 years. This is potentially offset by the improvement in disease control in the GHSG regimens, making them a more palatable option for the male patient, although a discussion of the potential effects of alkylators on fertility warrant patient input.

Conclusion

As the proportion of lymphoma patients surviving their initial diagnosis continues to expand, increasing effort will be required to individualize treatment to consider the potential late effects of therapy. As the cases illustrate, patient sex, age, preexisting risk factors, and—when RT is considered—the anatomic distribution of disease are all factors that need to be considered if sophisticated judgments are to be made about the trade-offs between treatment intensity and the risks of late toxicity.

At the foundation of treatment decisions is consideration of the risk of death from the primary lymphoma. This is well illustrated by contrasting the apparent risks of RT among patients with early-stage HL vs aggressive-histology NHL. Whereas the risk of RT-related second cancer among HL patients is well described, several studies have found no increase in the risk of second cancer associated with RT when given to patients with NHL.[44,77] In a European study of aggressive-histology NHL, for example, RT was not associated with an increased risk of second cancer even after adjusting for patient age, whereas salvage therapy did increase this risk.[56] This is almost certainly because lymphoma caused the large majority of patient deaths. This shows that simply reducing the intensity of initial treatment may not necessarily improve long-term outcomes in predictable ways for all patients. Important trials in both HL and NHL are exploring the use of response-adapted therapy to tailor treatment according to response to the initial chemotherapy cycles, and data are emerging regarding the genetic correlates of late toxicity, both of which hold promise to further refine (and complicate) lymphoma management.

Finally, optimizing treatment on an individual basis often requires understanding patients' perspectives on the relative value of treatment intensity, disease control, and the risks of late toxicity. Insofar as many treatment trade-offs are essentially value decisions and not medical requirements, patients' own views are an important contributor to selecting appropriate treatment.

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References

1. SEER cancer statistics review 1975-2011. National Cancer Institute's Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov/csr/1975_2011/results_merged/topic_survival_by_year_dx.pdf. Accessed January 6, 2015.
2. Darby SC, Cutter DJ, Boerma M, et al. Radiation-related heart disease: current knowledge and future prospects. *Int J Radiat Oncol Biol Phys*. 2010;76(3):656-665.
3. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood*. 2007;109(5):1878-1886.
4. Galper SL, Yu JB, Mauch PM, et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. *Blood*. 2011;117(2):412-418.
5. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA*. 1993;270(16):1949-1955.
6. Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood*. 2011;117(6):1806-1816.
7. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606.
8. Illidge T, Specht L, Yahalom J, et al; International Lymphoma Radiation Oncology Group. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2014;89(1):49-58.
9. Specht L, Yahalom J, Illidge T, et al; ILROG. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *Int J Radiat Oncol Biol Phys*. 2014;89(4):854-862.
10. Maraldo MV, Brodin NP, Aznar MC, et al. Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. *Ann Oncol*. 2013;24(8):2113-2118.
11. Charpentier AM, Conrad T, Sykes J, et al. Active breathing control for patients receiving mediastinal radiation therapy for lymphoma: impact on normal tissue dose. *Pract Radiat Oncol*. 2014;4(3):174-180.
12. Voong KR, McSpadden K, Pinnix CC, et al. Dosimetric advantages of a "butterfly" technique for intensity-modulated radiation therapy for young female patients with mediastinal Hodgkin's lymphoma. *Radiat Oncol*. 2014;9(1):94.
13. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):640-652.
14. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;97(11):2869-2879.
15. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst*. 2007;99(3):206-214.
16. Myrehaug S, Pintilie M, Tsang R, et al. Cardiac morbidity following modern treatment for Hodgkin lymphoma: supra-additive cardiotoxicity of doxorubicin and radiation therapy. *Leuk Lymphoma*. 2008;49(8):1486-1493.
17. Drafts BC, Twomley KM, D'Agostino R Jr, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging*. 2013;6(8):877-885.
18. Limat S, Daguindau E, Cahn JY, et al. Incidence and risk-factors of CHOP/R-CHOP-related cardiotoxicity in patients with aggressive non-Hodgkin's lymphoma. *J Clin Pharm Ther*. 2014;39(2):168-174.
19. Christiansen JR, Hamre H, Massey R, et al. Left ventricular function in long-term survivors of childhood lymphoma. *Am J Cardiol*. 2014;114(3):483-490.
20. Hershman DL, McBride RB, Eisenberger A, Tsai WY, Grann VR, Jacobson JS. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26(19):3159-3165.
21. Herbrecht R, Cernohous P, Engert A, et al. Comparison of pixantrone-based regimen (CPOP-R) with doxorubicin-based therapy (CHOP-R) for treatment of diffuse large B-cell lymphoma. *Ann Oncol*. 2013;24(10):2618-2623.
22. Glanzmann C, Kaufmann P, Jenni R, Hess OM, Huguenin P. Cardiac risk after mediastinal irradiation for Hodgkin's disease. *Radiother Oncol*. 1998;46(1):51-62.
23. King V, Constine LS, Clark D, et al. Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 1996;36(4):881-889.
24. Myrehaug S, Pintilie M, Yun L, et al. A population-based study of cardiac morbidity among Hodgkin lymphoma patients with preexisting heart disease. *Blood*. 2010;116(13):2237-2240.
25. Lorenzo Bermejo J, Pukkala E, Johannesen TB, Sundquist J, Hemminki K. Age-time risk patterns of solid cancers in 60 901 non-Hodgkin lymphoma survivors from Finland, Norway and Sweden. *Br J Haematol*. 2014;164(5):675-683.
26. van Leeuwen FE, Klokman WJ, Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *J Clin Oncol*. 2000;18(3):487-497.
27. Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst*. 2005;97(19):1428-1437.
28. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA*. 2003;290(4):465-475.
29. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst*. 2003;95(13):971-980.

30. Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol*. 2009;27(24):3901-3907.
31. Koh E, Tran T, Heydarian M, et al. A dosimetric study of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: implications for second cancer risk and cardiac toxicity. *In J Radiat Oncol Biol Phys.* 2005;63(suppl 1):S422-S423.
32. De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. *J Clin Oncol*. 2009;27(26):4239-4246.
33. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. *Ann Oncol*. 2006;17(12):1749-1760.
34. Campbell BA, Hornby C, Cunninghame J, et al. Minimising critical organ irradiation in limited stage Hodgkin lymphoma: a dosimetric study of the benefit of involved node radiotherapy. *Ann Oncol*. 2012;23(5):1259-1266.
35. Weber DC, Johanson S, Peguret N, Cozzi L, Olsen DR. Predicted risk of radiation-induced cancers after involved field and involved node radiotherapy with or without intensity modulation for early-stage hodgkin lymphoma in female patients. *Int J Radiat Oncol Biol Phys*. 2011;81(2):490-497.
36. Swerdlow AJ, Higgins CD, Smith P, et al. Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study. *J Clin Oncol*. 2011;29(31):4096-4104.
37. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol*. 2002;20(16):3484-3494.
38. Ibrahim EM, Kazkaz GA, Abouelkhair KM, et al. Increased risk of second lung cancer in Hodgkin's lymphoma survivors: a meta-analysis. *Lung*. 2013;191(1):117-134.
39. Bhatia S, Yasui Y, Robison LL, et al; Late Effects Study Group. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol*. 2003;21(23):4386-4394.
40. Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. *J Clin Oncol*. 2000;18(3):498-509.
41. Swerdlow AJ, Schoemaker MJ, Allerton R, et al. Lung cancer after Hodgkin's disease: a nested case-control study of the relation to treatment. *J Clin Oncol*. 2001;19(6):1610-1618.
42. Gilbert ES, Stovall M, Gospodarowicz M, et al. Lung cancer after treatment for Hodgkin's disease: focus on radiation effects. *Radiat Res*. 2003;159(2):161-173.
43. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst*. 2002;94(3):182-192.
44. Mudie NY, Swerdlow AJ, Higgins CD, et al. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. *J Clin Oncol*. 2006;24(10):1568-1574.
45. Curtis RE, Boice JD Jr, Stovall M, et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N Engl J Med*. 1992;326(26):1745-1751.
46. van Leeuwen FE, Chorus AM, van den Belt-Dusebout AW, et al. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. *J Clin Oncol*. 1994;12(5):1063-1073.
47. Schonfeld SJ, Gilbert ES, Dores GM, et al. Acute myeloid leukemia following Hodgkin lymphoma: a population-based study of 35,511 patients. *J Natl Cancer Inst*. 2006;98(3):215-218.
48. Valagussa P, Santoro A, Fossati Bellani F, Franchi F, Banfi A, Bonadonna G. Absence of treatment-induced second neoplasms after ABVD in Hodgkin's disease. *Blood*. 1982;59(3):488-494.
49. Pedersen-Bjergaard J, Daugaard G, Hansen SW, Philip P, Larsen SO, Rørth M. Increased risk of myelodysplasia and leukaemia after etoposide, cisplatin, and bleomycin for germ-cell tumours. *Lancet*. 1991;338(8763):359-363.
50. Cowell IG, Austin CA. Mechanism of generation of therapy related leukemia in response to anti-topoisomerase II agents. *Int J Environ Res Public Health*. 2012;9(6):2075-2091.
51. Eichenauer DA, Thielen I, Haverkamp H, et al. Therapy-related acute myeloid leukemia and myelodysplastic syndromes in patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group. *Blood*. 2014;123(11):1658-1664.
52. Tam CS, Seymour JF, Prince HM, et al. Treatment-related myelodysplasia following fludarabine combination chemotherapy. *Haematologica*. 2006;91(11):1546-1550.
53. Sacchi S, Marcheselli L, Bari A, et al. Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: a 16-year follow-up study. *Haematologica*. 2008;93(3):398-404.
54. Hake CR, Graubert TA, Fenske TS. Does autologous transplantation directly increase the risk of secondary leukemia in lymphoma patients? *Bone Marrow Transplant*. 2007;39(2):59-70.
55. Forrest DL, Hogge DE, Nevill TJ, et al. High-dose therapy and autologous hematopoietic stem-cell transplantation does not increase the risk of second neoplasms for patients with Hodgkin's lymphoma: a comparison of conventional therapy alone versus conventional therapy followed by autologous hematopoietic stem-cell transplantation. *J Clin Oncol*. 2005;23(31):7994-8002.
56. Moser EC, Noordijk EM, van Leeuwen FE, et al. Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study. *Haematologica*. 2006;91(11):1481-1488.
57. van Leeuwen FE, Klokman WJ. Re: Smoking, treatment for Hodgkin's disease, and subsequent lung cancer risk. *J Natl Cancer Inst*. 1996;88(3-4):209.
58. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol*. 2007;25(12):1489-1497.
59. Constine LS, Tarbell N, Hudson MM, et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. *Int J Radiat Oncol Biol Phys*. 2008;72(1):24-33.
60. Greaves P, Sarker SJ, Chowdhury K, et al. Fertility and sexual function in long-term survivors of haematological malignancy: using patient-reported outcome measures to assess a neglected area of need in the late effects clinic. *Br J Haematol*. 2014;164(4):526-535.
61. Biasoli I, Falorio S, Luminari S, Spector N, Federico M. Fertility in female survivors of Hodgkin's lymphoma. *Rev Bras Hematol Hemoter*. 2012;34(1):48-53.
62. Swerdlow AJ, Cooke R, Bates A, et al; England and Wales Hodgkin Lymphoma Follow-up Group. Risk of premature menopause after treatment for Hodgkin's lymphoma. *J Natl Cancer Inst*. 2014;106(9):dju207.
63. Behringer K, Mueller H, Goergen H, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. *J Clin Oncol*. 2013;31(2):231-239.
64. Hodgson DC, Pintilie M, Gitterman L, et al. Fertility among female hodgkin lymphoma survivors attempting pregnancy following ABVD chemotherapy. *Hematol Oncol*. 2007;25(1):11-15.
65. Anselmo AP, Cartoni C, Bellantuono P, Maurizi-Enrici R, Aboulkair N, Ermini M. Risk of infertility in patients with Hodgkin's disease treated with ABVD vs MOPP vs ABVD/MOPP. *Haematologica*. 1990;75(2):155-158.
66. Meissner J, Tichy D, Dietrich S, et al. Parenthood in long-term survivors after CHOP with or without etoposide treatment for aggressive lymphoma. *Br J Haematol*. 2014;166(4):612-615.
67. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med*. 2013;368(15):1408-1416.
68. Gharwan H, Dunleavy K, Shovlin M, et al. Study on the fertility status of females with primary mediastinal B-cell lymphoma following treatment with dose-adjusted EPOCH-rituximab [ASH abstract 1779]. *Blood.* 2013;112(21)(suppl).
69. von Tresckow B, Plütschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol*. 2012;30(9):907-913.
70. Carter A, Robison LL, Francisco L, et al. Prevalence of conception and pregnancy outcomes after hematopoietic cell transplantation: report from the Bone Marrow Transplant Survivor Study. *Bone Marrow Transplant*. 2006;37(11):1023-1029.
71. Brice P, Haioun C, André M, Gisselbrecht C; Groupe d'Etude des Lymphomes de l'Adulte. Pregnancies after high-dose chemotherapy and autologous stem cell transplantation in aggressive lymphomas. *Blood*. 2002;100(2):736.
72. Anserini P, Chiodi S, Spinelli S, et al. Semen analysis following allogeneic bone marrow transplantation. Additional data for evidence-based counselling. *Bone Marrow Transplant*. 2002;30(7):447-451.
73. Loren AW, Chow E, Jacobsohn DA, et al. Pregnancy after hematopoietic cell transplantation: a report from the late effects working committee of the Center for International Blood and Marrow Transplant Research (CIBMTR). *Biol Blood Marrow Transplant*. 2011;17(2):157-166.
74. Ibrahim EM, Abouelkhair KM, Kazkaz GA, Elmasri OA, Al-Foheidi M. Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis. *BMC Cancer*. 2012;12(1):197.
75. Horwich A, Swerdlow AJ. Second primary breast cancer after Hodgkin's disease. *Br J Cancer.* 2004;90(2):294-298.
76. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol.* 2014.
77. Sacchi S, Marcheselli L, Bari A, et al. Second malignancies after treatment of diffuse large B-cell non-Hodgkin's lymphoma: a GISL cohort study. *Haematologica.* 2008;93(9):1335-1342.