Review Article

Therapy-Related Late Adverse Events in Hodgkin's Lymphoma

Manuel Gotti,[1] Valeria Fiaccadori,[1] Elisa Bono,[1] Benedetta Landini,[1] Marzia Varettoni,[1] Luca Arcaini,[1,2] and Maurizio Bonfichi[1]

[1] *Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy*
[2] *Department of Molecular Medicine, University of Pavia, 27100 Pavia, Italy*

Correspondence should be addressed to Luca Arcaini; luca.arcaini@unipv.it

Hodgkin's lymphoma (HL) is one of the most curable hematologic diseases with an overall response rate over 80%. However, despite this therapeutic efficacy, HL survivors show a higher morbidity and mortality than other people of the same age because of long-term therapy-related events. In the last decades, many efforts have been made to reduce these effects through the reduction of chemotherapy dose, the use of less toxic chemotherapeutic agents, and the introduction of new radiation techniques. In this paper, we will describe the main long-term effects related to chemotherapy and radiotherapy for HL, the efforts to reduce toxicity made in the last years, and the clinical aspects which have to be taken into consideration in the followup of these patients.

1. Introduction

During the last decades, survival of patients (pts) treated for classical Hodgkin's lymphoma (HL) has improved substantially, getting nowadays to an overall cure rate of 80%–85%, with peaks of more than 90% in early stages.

Despite high rates of response, HL survivors have increased morbidity and mortality compared to the general population because of therapy-related side effects. Late complications of treatment are reported since the 70s and include cardiovascular diseases, lung diseases, endocrine abnormalities and secondary malignancies [1, 2].

The aim of this paper is to systematically summarize the available data on long-term events in patients treated for HL. To this aim, we performed a systematic PubMed search (http://www.pubmed.gov/) using the keywords "long-term events," "Hodgkin's lymphoma," and "late toxicity." All relevant articles were included and were reviewed with reference to cardiovascular and pulmonary diseases, thyroid and fertility dysfunctions, and second cancers related to chemotherapy and radiotherapy.

2. Cardiovascular Diseases

In HL pts treated with anthracyclines and/or mediastinal radiotherapy (RT), an increased mortality due to cardiac diseases has been frequently reported [3–5].

Anthracyclines can cause cardiomyopathy, valvular and conduction defects [6]. These clinical manifestations are caused by myocyte loss and interstitial fibrosis leading to decreased left ventricle (LV) contractility, reduced ventricular wall thickness, and progressive LV dilation. Cancer survivors who received anthracycline combined with RT treatment may have an impaired quality of life, develop heart failure, or eventually die for cardiac complications. Earlier studies have demonstrated that the risk of developing clinical heart failure 15 years after anthracycline therapy for childhood cancer was estimated to be approximately 5% [7].

Regarding this issue in HL, Swerdlow and colleagues analyzed a cohort of 7,033 HL patients treated in UK since 1967 to 2000 and found a higher risk of myocardial infarction, compared to the general population [8]; the risk of death from myocardial infarction reached a peak 15–19 years after

treatment and remained significantly increased until 25 years after treatment. Risks were statistically increased significantly and independently for patients who had been treated with anthracyclines and supradiaphragmatic radiotherapy and were particularly high for patients treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen.

In our experience with ABVD, the cumulative risks of cardiovascular events at 5 and 12 years are 5.5% and 14% respectively, with a median time of 67 months [2].

A recent study by Tsai et al. [9] demonstrated a persistent decrease in LV function among HL survivors who underwent mediastinal RT with or without chemotherapy and confirmed that anthracycline treatment deteriorates RT-associated long-term myocardial dysfunction. In this study, echocardiography was performed in 47 HL survivors more than 20 years after successful mediastinal RT (20 of them had been treated with doxorubicin containing regimens) and in 20 healthy controls. LV function was assessed by the LV ejection fraction and global longitudinal and circumferential strains. The global longitudinal strain was reduced in pts receiving anthracycline with mediastinal RT compared to the group receiving mediastinal radiotherapy alone or radiotherapy combined with chemotherapy regimens without anthracyclines. Both patient groups had reduced circumferential strain compared to the healthy controls.

As described by studies previously cited, RT itself can induce coronary artery disease, myocardial fibrosis leading to restrictive cardiomyopathy, valvular damage, and cardiac autonomic dysfunction. In order to reduce the toxicity, extension of the irradiation fields has been limited over the years. However, in pts with mediastinal disease, involved field RT (IFRT) reduces the overall cardiac dose compared with mantle RT, but not necessarily the dose to the proximal coronary arteries. This relates to the initial descriptions of IFRT, which included hilar and subcarinal lymph nodes for all cases with mediastinal disease, even if these sites were not involved. Treatment of these regions would typically encompass the superior third of the heart. Therefore, whereas IFRT may reduce the morbidity caused by damage to the valves and the microvasculature within the myocardium, it is not clear whether the risk of coronary artery disease will be substantially reduced among pts receiving mediastinal radiotherapy.

Many efforts have been made to reduce cardiotoxicity without reducing treatment efficacy: for example, involved-node RT (INRT) technique encompasses the postchemotherapy volumes of the initially involved nodes, not the entire nodal regions. For pts with anterior mediastinal disease, INRT often allows further reduction in normal tissue dose compared with IFRT, due to the exclusion of uninvolved hilar and subcarenal nodes. A small study comparing normal tissue doses delivered with IFRT and INRT found that the latter resulted in a reduction in mean heart dose of 50% [10].

Another way to reduce cardiotoxicity is to decrease chemotherapy and RT dosages in pts with favorable early-stage disease. In a recent study published by the German Hodgkin Study Group (GHSG), it was demonstrated that 2 cycles of ABVD combined with RT 20 gray (Gy) are less toxic than 4 cycles of ABVD and 30 Gy but comparable in term of outcome [11].

In pediatric and adult pts receiving potentially cardiotoxic chemotherapy, the American Heart Association recommends routinely performs echocardiography at baseline and at every recurrence (class I recommendation). Adult survivors should undergo screening evaluations every 5 years, and pts with abnormal results should be monitored yearly.

Moreover, also traditional cardiac risk factors (for instance diabetes, hypercholesterolemia, hypertension, and smoking) increase the risk of heart disease among HL survivors. In a study of pts undergoing mediastinal RT, Glanzmann et al. found that the risk of cardiac events was significantly increased only among those pts with cardiac risk factors [12]. Similarly, 2 other studies found that all pts who developed coronary artery disease after mediastinal RT had at least one conventional risk factor [13, 14]. It is therefore essential for cured HL pts to minimize the cardiovascular diseases risk factors.

3. Lung Diseases

The combination of mediastinal RT with chemotherapy including bleomycin is associated with an increased risk of pulmonary toxicity with a median interval of 18 months from the end of RT [2]. In a prospective study at Memorial Sloan-Kettering Cancer Centre, 60 pts received 6 cycles of ABVD and 30 of them received mantle or mediastinal RT [15]. Pulmonary function tests and symptoms evaluation were conducted before, during, and after completion of chemotherapy and RT and at various time points thereafter. During chemotherapy, cough and dyspnoea on exertion developed in half of pts and reduction in pulmonary function occurred in nearly one-third of them. Discontinuation of bleomycin was necessary in nearly one-quarter of the cases. Following chemotherapy, there was a significant decline in median forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO); in pts who received mantle or mediastinal RT, there was a further decline in FVC.

A study conducted on 32 pts with early-stage HL treated with 4 cycles of ABVD chemotherapy followed by mediastinal RT confirmed these data; a significant reduction in forced expiratory volume in 1 second (FEV1), forced expiratory flow at 25%–75% (FEF25–75%), total lung capacity (TLC), vital capacity (VC), and DLCO at the end of treatment was observed. Reduction in TLC, VC, and DLCO, mirror of a restrictive type pulmonary defect, persisted one year after the end of therapy [16].

The Bleomycin Lung Toxicity (BLT) has been described with low dose of bleomycin [17] but is rare with doses below 300 mg, principally in young patients with germ cell tumors and no risk factors. The precise pathogenetic process of bleomycin-induced fibrosis is yet to be demonstrated, but probably, this can be the sequence leading to endothelial and interstitial capillary oedema, pneumocytes type II proliferation and necrosis with surfactant overproduction and release, surfactant phagocytosis by alveolar macrophages

with consequent activation of fibroblasts production [18]. The clinical manifestation of bleomycin lung toxicity seems like a hypersensitivity reaction with fever, diffuse infiltrate at chest X-ray, and eosinophilia. Signs and symptoms consist of fever, tachypnea, bibasal rales, intercostals retraction, dyspnea, sputum, and thoracic, pleuritic, and substernal pain.

Frequency of pulmonary toxicity has been reported in the literature to be approximately 10% to 25%. Corticosteroids are the usual treatment, with some evidence of improvement [19]. In a recent retrospective multicenter analysis of the elderly HL by Evens et al. [20], an incidence of bleomycin lung toxicity (BLT) of 32% was observed, with an associated mortality rate of 25%; these data supported the association of BLT and risk factors such as older age, cumulative bleomycin dose, renal insufficiency, pulmonary radiation, underlying lung disease, and tobacco history, and the concomitant use of G-CSF (the incidence of BLT was 38% and 0% among pts receiving G-CSF versus patients who did not receive it, resp.) [21].

There is still no consensus on reducing or avoiding the use of bleomycin in these settings of patients. However, in order to reduce the pulmonary toxicity, it could be useful to reduce the extension of RT fields through the introduction of IN-RT technique and limit the dose of bleomycin in pts with other risk factors for BLT. A retrospective study from Martin and colleagues at Mayo Clinic showed that the omission of bleomycin in patients showing any kind of toxicity had no impact on both overall survival and progression-free survival [22]. The results of GHSG HD13 will clarify if administration of bleomycin can be avoided in early favourable HL patients. In this study, 2 cycles of ABVD (arm A) were compared to a dacarbazine-deleted variant (ABV, arm B), a bleomycin-deleted variant (AVD, arm C), and a variant in which both dacarbazine and bleomycin were deleted (AV, arm D) to determine the minimum required cytotoxic drugs; after an interim analysis, arms B and D were closed and now we are waiting for final results.

Also in combined modalities, bleomycin toxicity can be increased by the interaction with other agents. Regarding this issue, a phase I/II dose-escalation study in pts with advanced-stage HL was conducted at Cologne University Hospital to investigate a new potentially nonleukemogenic modified BEACOPP scheme named BAGCOPP (bleomycin, doxorubicin, gemcitabine, cyclophosphamide, vincristine, procarbazine, and prednisone): in this scheme gemcitabine replaces etoposide. Interestingly, the concomitant use of gemcitabine and bleomycin leads to severe pulmonary toxicity, advising against the replacement of etoposide with gemcitabine in the escalated BEACOPP [23].

The use of bleomycin with the new antibody-drug conjugate brentuximab vedotin seems to be contraindicated because of adverse pulmonary effects: in a clinical trial brentuximab plus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was compared with brentuximab plus doxorubicin, vinblastine, and dacarbazine (AVD) as front-line therapy for HL: noninfectious pulmonary toxicity developed in a high portion of pts (40%) in the brentuximab-ABVD group [24].

4. Thyroid Abnormalities

Thyroid abnormalities following mantle field or neck RT are observed in approximately 20%–30% of HL survivors and hypothyroidism caused by direct vascular damage to the thyroid gland is the most common event. Hancock et al. [25] studied 1,787 HL survivors treated at Stanford University from 1961 to 1989. The actuarial risk of thyroid disease in those who had mantle RT was 52% at 20 years after treatment, increasing to 67% at 25 years; the risk of developing hypothyroidism was 44% at 25 years after therapy for HL.

The risk of radiation-related thyroid dysfunction seems to be dose related [26, 27]. In a study from the University of Minnesota, the estimated actuarial risk of developing hypothyroidism was 60% at 11 years. In addition, the relative risk of hypothyroidism was estimated to increase by 1,02/Gy [28].

Indirect effects and central hypothyroidism due to involvement of hypothalamic-pituitary axis are less common, as well as Graves' disease (risk 3.3% at 20 years after therapy), benign adenoma, multinodular goiter, thyroiditis, and thyroid malignancies [29].

Moreover, in the Stanford study [25], HL survivors treated with mantle RT had a risk of thyroid cancer 16 times higher than the expected risk.

In our institution, the median time from the end of RT to dysthyroidism is 74 months (range: 27–107 months) with cumulative risks at 5 and 12 years of 2% and 7%, respectively [2].

The high frequency of thyroid disorders in pts treated with radiation to head and neck requires lifelong thyroid surveillance. Examination of the thyroid hormones and thyroid stimulating hormone (TSH) should be checked on an annual basis. TSH levels greater than 5 mU/L, even without overt clinical manifestations, require thyroid hormone replacement therapy to minimize clinical symptoms and development of benign and malignant thyroid nodules [30]. Pts with a palpable nodule require evaluation with Doppler ultrasonography, with further management based on imaging findings [31].

5. Male Fertility

Spermatogenesis lasts about 70 days; spermatogonia of type A in seminiferous epithelium duplicate to maintain the reserve, whereas type B spermatogonia divide into primary spermatocytes, that will first become spermatids and then spermatozoa. Cycle-specific chemotherapeutic agents may cause a temporary stop in spermatogenesis due to damage to type B spermatogonia, more sensitive to cytotoxic agents but not to spermatogonia of type A, characterized by a low mitotic index. Noncycle specific chemotherapeutic agents, such as alkylating agents, used at high doses, are more likely to cause azoospermia or long-term (up to 10 years after the end of chemotherapy) or even permanent depletion of type A spermatogonia. Spermatogenesis is sensitive to cyclophosphamide, procarbazine, and mechlorethamine (a nitrogen mustard), used in old treatment regimens such as MOPP and COPP (cyclophosphamide, vincristine, procarbazine, and

prednisone) and in the more recent BEACOPP, while other regimens without alkylating agents, such as ABVD, usually do not cause male infertility [32].

In a study from University Hospital Cologne, an increased risk for inadequate semen quality even before treatment was described, particularly in pts with elevated ESR and advanced disease stage. A more recent EORTC study [33] investigating sperm quality in untreated pts with early-stage HL showed an association between B symptoms and sperm quality.

Fertility counselling is indicated in patients prior to chemotherapy to evaluate the possibility of cryopreserving ejaculated sperm. However, this recommendation is not valid for patients with azoospermia; in this subset of patients testicular sperm extraction can be considered [34, 35].

6. Female Fertility

Risk of menstrual irregularities and female infertility is well known. As in male gender, the main cause of infertility seems to be the use of alkylating agents used in MOPP and BEACOPP regimens [36, 37]. Premature ovarian failure is defined as the premature (age < 40 years) termination of ovarian function. The loss of part or of the entire stock of primordial follicles leads to hypergonadotropic amenorrhea which causes infertility and symptoms of estrogen deprivation such as hot flushes, vaginal dryness, and dyspareunia.

After chemotherapy, recovery of normal menstrual cycles does not guarantee normal fertility, but amenorrhea is a strong negative predictor of fertility. There are several hormone assays to establish endocrine profile. The anti-Müllerian hormone (AMH) produced by growing follicles declines with age and is undetectable after menopause. Its level parallels that of the number of primordial follicles and seems to be the most informative determination [38]. Numerous studies have demonstrated the usefulness of transvaginal ultrasound in terms of determining ovarian volume and antral follicular count [39]. Even if there are no standard recommendations, combination of AMH dosage and transvaginal ultrasound should be advisable [40].

The GHSG evaluated women aged less than 40 years and treated between 1994 and 1998; half of women who received dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) developed secondary amenorrhea at a median followup of 3.2 years. The study also confirmed that older age at treatment increased risk of infertility [41]. ABVD regimen, on the other side, does not seem to lead to permanently impaired gonadic function [42]. Regarding the role of oral contraceptives (OC) in preserving fertility, data do not confirm that they succeed in protecting the ovarian reserve, in particular during chemotherapy regimens containing alkylating agents, while the role of GnRH analogues (GnRH-a) is still a matter of debate. In a randomized study published by GHSG, female pts (age range 18–40 years) were randomly assigned either to receive daily OC or monthly GnRH-a during escalated combination therapy with bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc). Hormonal levels (FSH, LH, estradiol,

inhibin B, AMH, progesterone, testosterone, and DHEAS) were determined at baseline, during therapy, and at followup. This study was closed prematurely after an interim analysis of 12 pts in arm treated with OC and 11 in arm B treated by GnRH-analogues. The anti-Müllerian hormone level after at least 12 months was reduced in all pts. For the entire study cohort, the respective ovarian follicle preservation rate was 0% [43, 44].

On the other hand, patients treated with 4 cycles of ABVD or 2 BEACOPPesc + 2 ABVD within the HD14 trial have recently presented and show that prophylactic use of GnRH-analogues has significant prognostic impact on preservation of fertility [45].

Optimal timing to address fertility issues is before initiation of treatment, and referral to a reproductive specialist is mandatory. Moreover, this counseling is recommended after treatment to monitor for premature menopause and initiation of calcium, vitamin D, bisphosphonates, and exercise for the treatment of bone demineralization [46].

Many HL experts recommend waiting 2 years after HL treatment to begin reproductive efforts, when the risk of relapse significantly decreases [47].

7. Second Cancer

Secondary malignancies are a leading cause of morbidity and mortality among long-term survivors of HL.

There is an overall 18-fold increased risk of developing secondary malignancies in HL survivors compared to the general population [48] and the cumulative incidence of second malignancy is higher when compared with pts treated for other cancers [49, 50].

Standards of treatment have been proposed as contributing to the high rate of secondary malignancies [51]; differences are observed between pts receiving chemotherapy and pts receiving chemoradiotherapy; moreover, in the chemotherapy only subgroup, difference is reported between pts treated with alkylating agents and pts receiving ABVD scheme.

Chemotherapy is linked to a substantial risk of developing mostly 3 malignancies: myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL) and lung cancer.

Second cancer risk peaks 5 to 9 years after chemotherapy alone; in particular chemotherapy-related MDS and AML occur within 10 years of treatment, with a median of 3 years, and are more likely to be caused by DNA-breaking alkylating agents, such as mechlorethamine and procarbazine in the MOPP regimen, and by topoisomerase II inhibitors, such as etoposide. Secondary MDS differ according to primary chemotherapy in terms of time to onset and cytogenetic abnormalities. MDS correlated to the use of alkylating agents show peaks of incidence between 5 and 10 years after chemotherapy and are associated to 7q–/–7 with mutations of *AML1*, 5q–/–5, mutation of *p53* and complex chromosome rearrangements [52]. On the other side, MDS correlated to the use of topoisomerase II inhibitors generally occur with a relatively short latency period and are associated to balanced translocations involving the chromosomal band 11q23,

resulting in chimerical rearrangements between the *MLL* gene and one of its numerous alternative partner genes [53].

With the introduction of the ABVD regimen, this risk has substantially been reduced, as we observed in our institution [54]. However, the main therapy-related risk factor is considered RT which is an integral part of HL treatment protocols. Pts receiving combined treatment including chemotherapy and RT are at higher risk for all the cited neoplasms plus other solid tumors, such as nonmelanomatous skin cancer and breast cancer.

It is well established that exposure to ionizing radiation increases the risk of solid tumors [55] and recent studies evaluating the long-term incidence of second malignancies in survivors of HL found a reduced incidence of second solid tumors in survivors of HL, treated without RT [56, 57]. In the British experience, relative risk (RR) of second cancer is much higher after combined modalities than after chemotherapy only (RR 3.9 versus 2) [53]. After combined modalities, second cancers have a longer latency period, with risk increasing after 15 to 19 years, with no plateau to the risk.

A particular subset of pts is characterized by young women receiving mediastinal RT; as is now well known they have a significantly increased risk of developing breast cancer. For women treated for HL before the age of 30 the risk of developing breast cancer is 6 times greater than in the general population, with an absolute excess risk of 20 to 40 occurrences per 10,000 annually. Most of this excess risk is attributed to irradiation of axillae and mediastinum, with relative risks varying by age at irradiation, radiation dose, and extent of radiation field. Women treated with RT in adolescent years have a significantly higher risk of developing breast cancer than those treated later in life. The increased rate of secondary breast cancers emerges following a latency of 10 years and persists beyond 25 years of followup [58–65].

A recent multi-institutional matched cohort study showed that breast cancer after RT for HL is more likely to be detected at an earlier stage, to be bilateral at diagnosis, with an increased risk of metachronous contralateral breast cancer [66].

Recent achievements in RT allow to utilize significantly lower doses of radiation and smaller fields, and this would hopefully reflect in a consistently decreased rate of secondary cancers, especially breast cancers, in the future; as a matter of fact women who received mantle field radiotherapy in the 80s and 90s need now to be carefully screened for early detecting of breast cancers.

8. Conclusions

In the last years, the use of chemotherapy regimens not containing alkylating agents and the reduction of the doses and the extent of the irradiation fields have led to decrease secondary effects in long term in HL survivors. However, these complications still play an important role in the therapeutic choice and in the followup of these pts and many efforts have to be made in reducing them without compromising the efficacy of the treatment.

References

[1] B. M. P. Aleman, A. W. van den Belt-Dusebout, W. J. Klokman, M. B. Van't Veer, H. Bartelink, and F. E. van Leeuwen, "Long-term cause-specific mortality of patients treated for Hodgkin's disease," *Journal of Clinical Oncology*, vol. 21, no. 18, pp. 3431–3439, 2003.

[2] E. Brusamolino, A. Baio, E. Orlandi et al., "Long-term events in adult patients with clinical stage IA-IIA nonbulky Hodgkin's lymphoma treated with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine and adjuvant radiotherapy: a single-institution 15-year follow-up," *Clinical Cancer Research*, vol. 12, no. 21, pp. 6487–6493, 2006.

[3] A. K. Ng, "Review of the cardiac long-term effects of therapy for Hodgkin lymphoma," *The British Journal of Haematology*, vol. 154, no. 1, pp. 23–31, 2011.

[4] B. M. P. Aleman, A. W. van den Belt-Dusebout, M. L. de Bruin et al., "Late cardiotoxicity after treatment for Hodgkin lymphoma," *Blood*, vol. 109, no. 5, pp. 1878–1886, 2007.

[5] S. Myrehaug, M. Pintilie, R. Tsang et al., "Cardiac morbidity following modern treatment for Hodgkin lymphoma: supra-additive cardiotoxicity of doxorubicin and radiation therapy," *Leukemia and Lymphoma*, vol. 49, no. 8, pp. 1486–1493, 2008.

[6] O. Hequet, Q. H. Le, I. Moullet et al., "Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults," *Journal of Clinical Oncology*, vol. 22, no. 10, pp. 1864–1871, 2004.

[7] L. C. M. Kremer, E. C. van Dalen, M. Offringa, and P. A. Voûte, "Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review," *Annals of Oncology*, vol. 13, no. 4, pp. 503–512, 2002.

[8] A. J. Swerdlow, C. D. Higgins, P. Smith et al., "Myocardial infarction mortality risk after treatment for hodgkin disease: a collaborative British cohort study," *Journal of the National Cancer Institute*, vol. 99, no. 3, pp. 206–214, 2007.

[9] H. R. Tsai, O. Gjesdal, T. Wethal et al., "Left ventricular function assessed by two-dimensional speckle tracking echocardiography in long-term survivors of hodgkin's lymphoma treated by mediastinal radiotherapy with or without anthracycline therapy," *The American Journal of Cardiology*, vol. 107, no. 3, pp. 472–477, 2011.

[10] D. C. Weber, N. Peguret, G. Dipasquale, and L. Cozzi, "Involved-node and involved-field volumetric modulated arc versus fixed beam intensity-modulated radiotherapy for female patients with early-stage supra-diaphragmatic Hodgkin lymphoma: a comparative planning study," *International Journal of Radiation Oncology Biology Physics*, vol. 75, no. 5, pp. 1578–1586, 2009.

[11] A. Engert, A. Plutschow, H. T. Eich et al., "Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma," *The New England Journal of Medicine*, vol. 363, no. 7, pp. 640–652, 2010.

[12] C. Glanzmann, P. Kaufmann, R. Jenni, O. M. Hess, and P. Huguenin, "Cardiac risk after mediastinal irradiation for Hodgkin's disease," *Radiotherapy and Oncology*, vol. 46, no. 1, pp. 51–62, 1998.

[13] M. C. Hull, C. G. Morris, C. J. Pepine, and N. P. Mendenhall, "Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy," *Journal of the American Medical Association*, vol. 290, no. 21, pp. 2831–2837, 2003.

[14] V. King, L. S. Constine, D. Clark et al., "Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease,"

International Journal of Radiation Oncology Biology Physics, vol. 36, no. 4, pp. 881–889, 1996.

[15] A. Hirsch, N. Vander Els, D. J. Straus et al., "Effect of ABVD chemotherapy with and without mantle or mediastinal irradiation on pulmonary function and symptoms in early-stage Hodgkin's disease," *Journal of Clinical Oncology*, vol. 14, no. 4, pp. 1297–1305, 1996.

[16] F. Villani, P. de Maria, V. Bonfante et al., "Late pulmonary toxicity after treatment for Hodgkin's disease," *Anticancer Research*, vol. 17, no. 6D, pp. 4739–4742, 1997.

[17] H. D. Sostman, R. A. Matthay, and C. E. Putman, "Cytotoxic drug induced lung disease," *The American Journal of Medicine*, vol. 62, no. 4, pp. 608–615, 1977.

[18] E. Azambuja, J. F. Fleck, R. G. Batista, and S. S. Menna Barreto, "Bleomycin lung toxicity: who are the patients with increased risk?" *Pulmonary Pharmacology and Therapeutics*, vol. 18, no. 5, pp. 363–366, 2005.

[19] FDA Drug Safety Communication, New Boxed Warning and Contraindication for Adcetris (brentuximab vedotin).

[20] A. M. Evens, I. Helenowski, E. Ramsdale, : et al., "A retrospective multicenter analysis of elderly Hodgkin lymphoma: outcomes and prognostic factors in the modern era," *Blood*, vol. 119, no. 3, pp. 692–695, 2012.

[21] E. Azoulay, S. Herigault, M. Levame et al., "Effect of granulocyte colony-stimulating factor on bleomycin-induced acute lung injury and pulmonary fibrosis," *Critical Care Medicine*, vol. 31, no. 5, pp. 1442–1448, 2003.

[22] W. G. Martin, K. M. Ristow, T. M. Habermann, J. P. Colgan, T. E. Witzig, and S. M. Ansell, "Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma," *Journal of Clinical Oncology*, vol. 23, no. 30, pp. 7614–7620, 2005.

[23] H. Bredenfeld, J. Franklin, L. Nogova et al., "Severe pulmonary toxicity in patients with advanced-stage hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's lymphoma study group," *Journal of Clinical Oncology*, vol. 22, no. 12, pp. 2424–2429, 2004.

[24] A. Younes, J. M. Connors, S. I. Park et al., "Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma," *ASH Annual Meeting Abstracts*, vol. 118, article 955, 2011.

[25] S. L. Hancock, R. S. Cox, and I. R. McDougall, "Thyroid diseases after treatment of Hodgkin's disease," *The New England Journal of Medicine*, vol. 325, no. 9, pp. 599–605, 1991.

[26] L. S. Constine, S. S. Donaldson, and I. R. McDougall, "Thyroid dysfunction after radiotherapy in children with Hodgkin's disease," *Cancer*, vol. 53, no. 4, pp. 878–883, 1984.

[27] C. Sklar, J. Whitton, A. Mertens et al., "Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the childhood cancer survivor study," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 9, pp. 3227–3232, 2000.

[28] S. Bhatia, N. K. C. Ramsay, J. P. Bantle, A. Mertens, and L. L. Robison, "Thyroid abnormalities after therapy for hodgkin's disease in childhood," *Oncologist*, vol. 1, no. 1-2, pp. 62–67, 1996.

[29] B. A. Jereczek-Fossa, D. Alterio, J. Jassem, B. Gibelli, N. Tradati, and R. Orecchia, "Radiotherapy-induced thyroid disorders," *Cancer Treatment Reviews*, vol. 30, no. 4, pp. 369–384, 2004.

[30] I. Solt, D. Gaitini, M. Pery et al., "Comparing thyroid ultrasonography to thyroid function in long-term survivors of childhood lymphoma," *Medical and Pediatric Oncology*, vol. 35, no. 1, pp. 35–40, 2000.

[31] M. L. Metzger, S. C. Howard, M. M. Hudson et al., "Natural history of thyroid nodules in survivors of pediatric Hodgkin lymphoma," *Pediatric Blood and Cancer*, vol. 46, no. 3, pp. 314–319, 2006.

[32] M. A. E. van der Kaaij, N. Heutte, N. le Stang et al., "Gonadal function in males after chemotherapy for early-stage Hodgkin's lymphoma treated in four subsequent trials by the European Organisation for Research and Treatment of Cancer: EORTC lymphoma group and the groupe d'Étude des lymphomes de l'adulte," *Journal of Clinical Oncology*, vol. 25, no. 19, pp. 2825–2832, 2007.

[33] M. A. E. van der Kaaij, N. Heutte, J. van Echten-Arends et al., "Sperm quality before treatment in patients with early stage Hodgkin's lymphoma enrolled in EORTC-GELA lymphoma group trials," *Haematologica*, vol. 94, no. 12, pp. 1691–1697, 2009.

[34] U. Rueffer, K. Breuer, A. Josting et al., "Male gonadal dysfunction in patients with Hodgkin's disease prior to treatment," *Annals of Oncology*, vol. 12, no. 9, pp. 1307–1311, 2001.

[35] M. Schrader, M. Müller, N. Sofikitis, C. Goessl, B. Straub, and K. Miller, "Testicular sperm extraction prior to treatment in azoospermic patients with Hodgkin's disease," *Annals of Oncology*, vol. 13, no. 2, p. 333, 2002.

[36] D. Meirow and D. Nugent, "The effects of radiotherapy and chemotherapy on female reproduction," *Human Reproduction Update*, vol. 7, no. 6, pp. 535–543, 2001.

[37] C. Bokemeyer, H. J. Schmoll, J. van Rhee, M. Kuczyk, F. Schuppert, and H. Poliwoda, "Long-term gonadal toxicity after therapy for Hodgkin's and non-Hodgkin's lymphoma," *Annals of Hematology*, vol. 68, no. 3, pp. 105–110, 1994.

[38] R. D. van Beek, M. M. van den Heuvel-Eibrink, J. S. E. Laven et al., "Anti-Müllerian hormone is a sensitive serum marker for gonadal function in women treated for Hodgkin's lymphoma during childhood," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 10, pp. 3869–3874, 2007.

[39] F. J. Broekmans, M. J. Faddy, G. Scheffer, and E. R. Te Velde, "Antral follicle counts are related to age at natural fertility loss and age at menopause," *Menopause*, vol. 11, no. 6, Part 1 of 2, pp. 607–614, 2004.

[40] S. Harel, C. Fermé, and C. Poirot, "Management of fertility in patients treated for Hodgkin's lymphoma," *Haematologica*, vol. 96, no. 11, pp. 1692–1699, 2011.

[41] K. Behringer, K. Breuer, T. Reineke et al., "Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's lymphoma study group," *Journal of Clinical Oncology*, vol. 23, no. 30, pp. 7555–7564, 2005.

[42] S. Viviani, A. Santoro, and G. Ragni, "Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD," *The European Journal of Cancer and Clinical Oncology*, vol. 21, no. 5, pp. 601–605, 1985.

[43] K. Behringer, L. Wildt, H. Mueller et al., "No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma. Final results of a phase II trial from the German Hodgkin Study Group," *Annals of Oncology*, vol. 21, no. 10, pp. 2052–2060, 2010.

[44] M. A. van der Kaaij, N. Heutte, P. Meijnders et al., "Premature ovarian failure and fertility in long-term survivors of Hodgkin's lymphoma: a European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'Etude des Lymphomes de l'Adulte Cohort Study," *Journal of Clinical Oncology*, vol. 30, no. 3, pp. 291–299, 2012.

[45] K. Behringer, I. Thielen, H. Mueller et al., "Fertility and gonadal function in female survivors after treatment of early unfavorable Hodgkin lymphoma (HL) within the German Hodgkin Study Group HD14 trial," *Annals of Oncology*, vol. 23, no. 7, pp. 1818–1825, 2012.

[46] J. R. Redman, D. R. Bajorunas, G. Wong et al., "Bone mineralization in women following successful treatment of Hodgkin's disease," *The American Journal of Medicine*, vol. 85, no. 1, pp. 65–72, 1988.

[47] C. A. Thompson, K. Mauck, R. Havyer et al., "Care of the adult Hodgkin lymphoma survivor," *The American Journal of Medicine*, vol. 124, no. 12, pp. 1106–1112, 2011.

[48] S. Bhatia, L. L. Robison, O. Oberlin et al., "Breast cancer and other second neoplasms after childhood Hodgkin's disease," *The New England Journal of Medicine*, vol. 334, no. 12, pp. 745–751, 1996.

[49] A. T. Meadows, D. L. Friedman, J. P. Neglia et al., "Second neoplasms in survivors of childhood cancer: findings from the childhood cancer survivor study cohort," *Journal of Clinical Oncology*, vol. 27, no. 14, pp. 2356–2362, 2009.

[50] A. C. MacArthur, J. J. Spinelli, P. C. Rogers, K. J. Goddard, N. Phillips, and M. L. McBride, "Risk of a second malignant neoplasm among 5-year survivors of cancer in childhood and adolescence in British Columbia, Canada," *Pediatric Blood and Cancer*, vol. 48, no. 4, pp. 453–459, 2007.

[51] A. J. Swerdlow, A. J. Douglas, G. V. Hudson, M. H. Bennett, and K. A. MacLennan, "Risk of second primary cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British national lymphoma investigation," *The British Medical Journal*, vol. 304, no. 6835, pp. 1137–1143, 1992.

[52] D. H. Christiansen, M. K. Andersen, and J. Pedersen-Bjergaard, "Mutations of AML1 are common in therapy-related myelodysplasia following therapy with alkylating agents and are significantly associated with deletion or loss of chromosome arm 7q and with subsequent leukemic transformation," *Blood*, vol. 104, no. 5, pp. 1474–1481, 2004.

[53] D. T. Bowen, M. E. Frew, R. Hills et al., "RAS mutation in acute myeloid leukemia is associated with distinct cytogenetic subgroups but does not influence outcome in patients younger than 60 years," *Blood*, vol. 106, no. 6, pp. 2113–2119, 2005.

[54] E. Brusamolino, M. Gotti, and V. Fiaccadori, "The risk of therapy-related myelodysplasia/acute myeloid leukemia in Hodgkin lymphoma has substantially decreased in the ABVD era abolishing mechlorethamine and procarbazine and limiting volumes and doses of radiotherapy," *Mediterranean Journal of Hematology and Infectious Diseases*, vol. 4, no. 1, Article ID e2012022, 2012.

[55] D. L. Preston, E. Ron, S. Tokuoka et al., "Solid cancer incidence in atomic bomb survivors: 1958–1998," *Radiation Research*, vol. 168, no. 1, pp. 1–64, 2007.

[56] P. M. Barbaro, K. Johnston, L. Dalla-Pozza et al., "Reduced incidence of second solid tumors in survivors of childhood Hodgkin's lymphoma treated without radiation therapy," *Annals of Oncology*, vol. 22, no. 12, pp. 2569–2574, 2011.

[57] A. J. Swerdlow, C. D. Higgins, P. Smith et al., "Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study," *Journal of Clinical Oncology*, vol. 29, no. 31, pp. 4096–4104, 2011.

[58] G. M. Dores, C. Metayer, R. E. Curtis et al., "Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years," *Journal of Clinical Oncology*, vol. 20, no. 16, pp. 3484–3494, 2002.

[59] D. C. Hodgson, E. S. Gilbert, G. M. Dores et al., "Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma," *Journal of Clinical Oncology*, vol. 25, no. 12, pp. 1489–1497, 2007.

[60] A. Horwich and A. J. Swerdlow, "Second primary breast cancer after Hodgkin's disease," *The British Journal of Cancer*, vol. 90, no. 2, pp. 294–298, 2004.

[61] D. C. Hodgson, E.-S. Koh, T. H. Tran et al., "Individualized estimates of second cancer risks after contemporary radiation therapy for Hodgkin lymphoma," *Cancer*, vol. 110, no. 11, pp. 2576–2586, 2007.

[62] S. L. Hancock, M. A. Tucker, and R. T. Hoppe, "Breast cancer after treatment of Hodgkin's disease," *Journal of the National Cancer Institute*, vol. 85, no. 1, pp. 25–31, 1993.

[63] M. L. de Bruin, J. Sparidans, M. B. Van't Veer et al., "Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes," *Journal of Clinical Oncology*, vol. 27, no. 26, pp. 4239–4246, 2009.

[64] L. B. Travis, D. A. Hill, G. M. Dores et al., "Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease," *Journal of the American Medical Association*, vol. 290, no. 4, pp. 465–475, 2003.

[65] F. E. van Leeuwen, W. J. Klokman, M. Stovall et al., "Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease," *Journal of the National Cancer Institute*, vol. 95, no. 13, pp. 971–980, 2003.

[66] E. B. Elkin, M. L. Klem, A. M. Gonzales et al., "Characteristics and outcomes of breast cancer in women with and without a history of radiation for Hodgkin's lymphoma: a multi-institutional, matched cohort study," *Journal of Clinical Oncology*, vol. 29, no. 18, pp. 2466–2473, 2011.

The Scientific
World Journal

Gastroenterology
Research and Practice

MEDIATORS
of
INFLAMMATION

Journal of
Diabetes Research

Disease Markers

Journal of
Immunology Research

International Journal of
Endocrinology

PPAR Research

Submit your manuscripts at
http://www.hindawi.com

BioMed
Research International

Journal of
Ophthalmology

Stem Cells
International

Evidence-Based
Complementary and
Alternative Medicine

Journal of
Obesity

Journal of
Oncology

Computational and
Mathematical Methods
in Medicine

Behavioural
Neurology

Parkinson's
Disease

AIDS
Research and Treatment

Oxidative Medicine and
Cellular Longevity