Review Article

Therapy-Related Late Adverse Events in Hodgkin’s Lymphoma

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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 anthracyclines 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 inspiratory 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 subternal 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, gemicitabine, cyclophosphamide, vincristine, procarbazine, and prednione): in this scheme gemicitabine replaces etoposide. Interestingly, the concomitant use of gemicitabine and bleomycin leads to severe pulmonary toxicity, advising against the replacement of etoposide with gemicitabine 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 spermatooza. 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
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 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].

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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 metastachronous 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


