VIA MEDICA

REVIEW ARTICLE

Paweł Kurczab[1, 12], Anna Czyż[2, 12], Elżbieta Turska[3], Joanna Drozd-Sokołowska[4, 12], Edyta Subocz[5, 12], Agnieszka Szymczyk[6], Waldemar Tomczak[7], Jadwiga Hołojda[8], Wojciech Jurczak[9, 12], Jan Walewski[10, 12], Jan Maciej Zaucha[11, 12]

[1]Oddział Chemioterapii Podkarpackiego Ośrodka Onkologicznego w Brzozowie; Poradnia Onkologiczna z Oddziałem Chemioterapii Dziennej NZOZ Mrukmed w Rzeszowie; Sekcja Chłoniaka Hodgkina Polskiej Grupy Badawczej Chłoniaków
[2]Klinika Hematologii i Chorób Rozrostowych Układu Krwiotwórczego Uniwersytetu Medycznego w Poznaniu
[3]Oddział Chemioterapii Regionalnego Ośrodka Onkologicznego w Łodzi
[4]Klinika Chorób Wewnętrznych, Hematologii i Onkologii Warszawskiego Uniwersytetu Medycznego; Sekcja Chłoniaka Hodgkina Polskiej Grupy Badawczej Chłoniaków
[5]Klinika Chorób Wewnętrznych i Hematologii Wojskowego Instytutu Medycznego w Warszawie; Sekcja Chłoniaka Hodgkina Polskiej Grupy Badawczej Chłoniaków
[6]Klinika Hematoonkologii i Transplantacji Szpiku Uniwersytetu Medycznego w Lublinie
[7]Klinika Hematoonkologii i Transplantacji Szpiku Uniwersytetu Medycznego w Lublinie; Katedra Interny z Zakładem Pielęgniarstwa Internistycznego Uniwersytetu Medycznego w Lublinie
[8]Oddział Hematologii Wojewódzkiego Szpitala Specjalistycznego w Legnicy
[9]Klinika Hematologii *Collegium Medicum* Uniwersytetu Jagiellońskiego w Krakowie
[10]Klinika Nowotworów Układu Chłonnego Centrum Onkologii — Instytutu w Warszawie; Sekcja Chłoniaka Hodgkina Polskiej Grupy Badawczej Chłoniaków
[11]Oddział Onkologii i Radioterapii Gdyńskiego Centrum Onkologii w Gdyni; Zakład Propedeutyki Onkologii Gdańskiego Uniwersytetu Medycznego;
[12]Sekcja Chłoniaka Hodgkina Polskiej Grupy Badawczej Chłoniaków

Early and late follow-up of patients with Hodgkin's lymphoma. Recommendations of the Polish Lymphoma Research Group

Address for correspondence:

Prof. dr hab. n. med. Jan Maciej Zaucha
Oddział Onkologii i Radioterapii
Gdyńskiego Centrum Onkologii w Gdyni
Zakład Propedeutyki Onkologii Gdańskiego
Uniwersytetu Medycznego
e-mail: jzaucha@gumed.edu.pl

Oncology in Clinical Practice
2015, Vol. 11, No. 6, 300–309
Translation: Piotr Hołownia, PhD

ISSN 2450–1654
www.opk.viamedica.pl

ABSTRACT

Post-treatment follow-up of patients with Hodgkin's lymphoma has not yet been fully optimised and is still based mainly on clinical practice and experience. During the first years of follow-up, the principal aims are to detect relapse and monitor any post-treatment complications or side effects. Such as they are, current guidelines on follow-up are herein considered and discussed, together with those now recommended by the Polish Lymphoma Research Group.

Key words: Hodgkin's lymphoma, follow-up, relapse, adverse events of treatment

Oncol Clin Pract 2015; 11, 6: 300–309

Introduction

Annual rates of Hodgkin's lymphoma (HL) are about 2–3 cases/100,000 population, being slightly higher in men [1]. Prognosis is relatively favourable, with around 80% of HL patients (respectively 90% and 70% for early and late stage HL) achieving durable remission [2]. In relapse, effective treatment may be given again to achieve remission. The potential risk of a relapse is a major problem for patients, although such risk in patients who achieve complete metabolic response (CMR) is somewhat small: 5–10% and 20%, respectively, for the early and late stages. For such reasons it is important to develop the principles for optimal patient follow-up so as to balance disease management with the expectations of patients. This process should take into account the ef-

fectiveness of additional testing in detecting recurrence and complications of treatment, its toxicity, and effect on quality of life, as well as the costs incurred. Procedures of patient follow-up after treatment are not established, and are based primarily on the experience of the treating physician and treatment practices at each care provider centre. There is very little scientific data testing ways of monitoring these patients during follow-up. During the first years of observation, greater emphasis is placed on detecting any recurrence of the disease, than monitoring long-term complications of therapy that becomes of greater importance later on.

Detecting HL recurrence

In the first 10–15 years of observation, the main cause of patient death is lymphoma itself [3–5], with recurrence usually occurring within three years after starting treatment; mostly (80%) in the first 18 months [3, 5]. A higher risk of recurrence is observed with the non-classical HL type, in which relapse may occur even after many years after treatment, sometimes in the form of transformation into T-cell/histiocyte-rich B-cell lymphoma. A thorough physical examination plays a major role in detecting recurrences, but consultation with the physician enables detection even up to 45–80% cases [3, 4, 6], whereas the physical examination yields a 10% detection rate. The most common symptoms reported by patients are new lymph node lesions appearing, coughing, and generalised symptoms and pain, often similar to those observed at the time of diagnosis [3–5].

While the need for a thorough history taking and physical examination is never in doubt, determination of the most apropriate lab tests for asymptomatic patients is difficult. According to the literature, routine laboratory tests such as measuring blood cell count, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and serum C-reactive protein (CRP) allows detection of relapse only in individual cases [4, 6]. However, abnormal results from additional tests in conjunction with clinical symptoms may justify performing imaging tests for confirming any suspicions of relapse.

Data on the effectiveness of imaging tests in the detection of relapse in asymptomatic patients are not clear. Routine chest X-ray examination detects recurrence in 5–23% of patients with relapsed HL [3, 4, 6]. This, however, requires multiple repetitive examinations. For example, one study demonstrated a detection rate for recurrence of 26 for 10,000 examinations in patients with early stages treated with radiotherapy (RT) [4]. Another study with 544 images showed that only 4 detected actual recurrence; in seven of these the test was false positive [6]. Furthermore, routine computed tomography (CT) is not recognised as a recommended procedure for monitoring patients. Although some studies showwed that CT allowed to detect more than 55% recurrence [7], others only showed a detection rate of 9% [6], with 2 true positive tests and 12 false positives when routine CT was performed in 211 patients; accounting for nearly 30% of costs for all patient visits and clinical evaluation.

Similar outcomes are found when using positron emission tomography in conjunction with computed tomography (PET/CT), although the data on this are rather limited and sometimes contradictory. In one study PET/CT was performed after 6, 12, 18, and 24 months and then once a year — 41 out of 51 (80%) recurrences were detected in 160 followed-up patients, whilst CT alone detected a 73% relapse rate, in the absence of symptoms in 31% of patients [8]. Above all, recurrence was detected mainly in patients with unfavourable prognostic factors (positive PET outcomes after 2 cycles of chemotherapy). In a Czech study, in which the decision to undertake PET/CT was dependent on the physician's judgment [9], 155 tests were performed in 67 asymptomatic patients, in which 18 turned out to be positive, but only in 6 cases lymphoma confirmed (5 HL recurrences and one lung cancer). Twelve investigations turned out to be false positive, where 9 showed inflammatory lesions, one a lesion after radiotherapy, and the rest had hyperplasia of the thymus and bone osteonecrosis of the hip. The predictive value (i.e. positive predictive value, PPV) was thus only 33%. This work highlights the importance of negative PET/CT results in patients with clinical symptoms suggestive of recurrence: in 16 of 27 patients with a negative PET a local recurrence was excluded (none of them relapsing) and that out of 11 positive tests, cancer was confirmed in 5 patients (constituting 18.5% of all those studied; comprising 4 relapsed HL cases and 1 follicular lymphoma). Similar findings were obtained in a Danish study, (routine PET/CT was performed 3 or 4 times over 2 years), where a positive PPV after routine PET scans was only 22% [10]. Interestingly, this analysis demonstrated a statistically significant greater proportion of false-positive results from routine examination in patients with non-classical Hodgkin's lymphoma. Patients in whom routine PET/CT had significantly higher PPV could also be identified. These were patients who had at least one of the following risk factors: primary extra-nodal involvement or positive test by PET during therapy, or residual uptake determined by PET after treatment (PPV being 36% vs. 5% in patients with no risk factors). The positive PPV in these patients almost equaled those seen in a group of patients undergoing PET/CT because of their clinical symptoms. For all true positives measured by PET/CT (both routine and based on symptoms), 71% were found in the first year, of whom 100% showed lesions in places originally occupied by the lymphoma. Other studies demonstrated similar results [11, 12];

Table 1. Mean values of effective dose received by the average adult patient during selected radiological studies. Available at http://www.radiologyinfo.org

Test procedure	Approximate effective dose	Natural radiation exposure equivalent
Dental X-ray	0.005 mSv[1]	1 day
Chest X-ray	0.1 mSv	10 days
Mammography	0.4 mSv	7 weeks
Spine X-ray	1.5 mSv	6 months
Small-dose chest CT	1.5 mSv	6 months
Head CT	2 mSv	8 months
Chest CT	7 mSv	2 years
Pelvic & abdominal CT	10 mSv	3 years
Pelvic and abdominal CT (2 phase)	20 mSv	7 years

[1]Average annual dose per person received from natural radiation in Poland is ≈ 2.5 mSv

however, the cost of such monitoring was very high. For example, a study by Petrausch et al. showed the need for performing an average of 8.3 tests for detection of 1 relapse in asymptomatic patients, whilst in symptomatic patients only 1.59 studies were required [13]. The study also identified following risk factors for recurrence: for a relapse up to 24 months, the presence of residual mass (visible by CT after treatment and defined as a lesion that has regressed by at least 75% but was still > 1.5 cm), whereas for relapse after 2 years, an initially advanced stage of the disease and the presence of clinical symptoms at the time of relapse.

It is noteworthy that despite identification of risk factors of disease recurrence, that is associated with high PPV of PET, no prospective study has shown evidence of improvements of patients' outcome after salvage treatment following early detection of recurrence in asymptomatic patients. Another study has demonstrated no significant differences in overall survival (OS) or disease-free survival in relapsed HL patients treated with high-dose therapy supported by autologous haematopoietic stem cell transplantation, between those diagnosed to be asymptomatic (based on imaging studies) and a group showing clinical symptoms (compared to patients according to risk factors) [14]. This observation was also consistent with studies in pediatric patients [15, 16]. In a further study, no significant differences were seen in relapse rate, progression-free survival, or OS between a patient group with routinely performed imaging studies compared to a patient group in which CT or PET/CT was performed in symptomatic patients [17]. It should be mentioned that patients from this study had no residual mass in the post-treatment evaluation. The numbers of imaging tests, and therefore the cost of detecting recurrence, was 10 times higher in the former patient group.

Due to the high costs of using PET/CT during the follow-up, a randomised study was undertaken to compare the value (cost/benefit analysis) of PET/CT with a combination of standard ultrasonography and chest X-ray in patients with an advanced stage of the disease. The sensitivity in detecting recurrence was comparable for both procedures; however, a significantly higher specificity and PPV (91% vs. 73%) was observed for the combined ultrasound and chest X-ray procedure, together with an incomparably lower toxicity [18].

In conclusion, imaging (in particular PET/CT) for all asymptomatic patients is thus currently not recommended. This is supported by several arguments. Firstly, the risk of relapse is relatively small, and furthermore the cumulative toxicity is clinically significant. Exposure to ionising radiation is associated with an increased cancer risk. An international study [19] demonstrated a 7.3% increase in cancer mortality in workers exposed to ionising radiation exceeding 75 mSv. When evaluating exposure to ionising radiation from diagnostic procedures, a retrospective study [20] on 486 lymphoma patients found that the average total effective dose (i.e. the dose defining whole body exposure to radiation) was 69 mSv per patient, where 46% patients received a dose above 75 mSv, and 14% above 150 mSv. As a comparison, the average annual dose received from exposure to natural radiation for a Polish person is around 2.5 mSv and for example radiation dose received during a single CT scan of the chest corresponds to a two-year cumulative dose of natural radiation (Table 1). Another argument against performing imaging studies for asymptomatic patients is the absence of any evidence that early detection of relapse is associated with a better prognosis. Finally, such procedures will adversely affect the quality of life of patients who are unnecessarily disturbed/worried by being reminded about the possibility of relapse. Furthermore, those with positive results will be exposed to additional and redundant procedures. The literature shows that there is a group of patients with risk factors, who could benefit from such a procedure, but this

Table 2. The relative risk (RR) of some solid tumours after treatment for Hodgkin's lymphoma. Based on the analysis of 18,862 patients [21]

Tumour location	Number of tumours/18,862 patients	RR[1]	Number of excess tumours
All solid cancers	1490		850.4
Women' breasts	277	6.1[2]	174.8
Lung	306	6.7	225.5
Pleura	6	19.5	5.4
Thyroid	40	3.1[3]	29.2
Stomach	64	9.5	46.1
Colon	110	4.3	53.5
Rectum & anus	35	1.8	8.8
Pancreas	33	4.7	18.5
Bladder	42	1.0	8.9
Kidneys	32	3.1	14.7
Soft tissue & bone	49	11.7	44.3
Prostate	104	1.0	11.5
Head/Neck tumours	69	5.1	49.1
Brain	33	1.8	15.6
Melanoma	54	1.6	23
Undefined primary localisation	70	10.6	51.8

[1]Joint RR for men, women, and for those diagnosed with HL at 30 yrs who reached 40 to 60 yrs (10–30 years since diagnosis) for all malignancies, except for breast cancer in women and thyroid cancer; [2]RR in women diagnosed with HL at 30 years of age having reached 40 years of age; [3]RR at HL diagnosis at 30 years of age and for all attained ages (RR at diagnosis for 20 years of age was 8.7, and 1.55 at 40 years)

requires confirmation by prospective investigations. It should be stressed, however, that introducing new drugs into treatment, such as brentuximab vedotin (BV), or anti-PD-1 (programmed cell death protein 1) and anti-PD-L1 (programmed cell death protein ligand-1) may change the role and place of imaging studies used in daily practice.

Monitoring the secondary complications of cancer therapy

For HL patients after treatment there is an increased risk of secondary tumours [5], which are the main cause of death after many years from treatment completion [21, 22]. The peak incidence after chemotherapy alone occurs 5–9 years after the end of treatment, after which the risk significantly decreases, whereas for combined treatment (with RT) the risk increases steadily for 20 years and remains levated even after 25 years ince end a therapy [23]. These are confirmed by the results of the study of 19,000 people that showed the similar solid tumour rates after end of treatment [22]. More than half (57%) of cancers occurred more often, compared to predicted numbers in the general population. Among other findings, the relative risk (RR) of breast and lung cancer were increased and also other cancers above and below the diaghram (supra/sub-phrenic). The risk was significantly increased in all evaluated locations of tumours, except the bladder and prostate, with the largest increase being for mesotheliomas (20-fold); Table 2. This was age-dependent: on the age at diagnosis of HL and the age currently attained by the patient (for most locations the risk was highest when HL was diagnosed at a younger age). The risk was increased, although in a different degree, regardless of the initial treatment, (details on the use of certain cytostatic drugs, the RT, and rescue/salvage therapy were not available). An interesting and practically important observation was that for younger HL patients, the risk of breast cancer and colon cancer was increased 10 to 25 years before the age at which routine screening is recommended.

The risk of secondary tumours is significantly increased by RT. A meta-analysis conducted by Franklin et al. [24] showed that when combined therapy is compared to RT alone, lower cancer rates are observed in the former, most probably due to fewer recurrences that would have required intensive and toxic rescue therapy. Adding RT for systemically treating patients with advanced HL increases the risk of a second tumour (at borderline significance); however, this was not observed in patients during early stages of the disease. The types of irradia-

tion were also compared: extended-field radiotherapy (EFRT) versus involved-field radiotherapy (IFRT), he breast cancer rates in patients undergoing EFRT was much higher compared to IFRT, but with no differences compared to other cancers.

A British study [23], comparing patients who received either chemotherapy alone or combined therapy, showed that the risk RR is greater in the latter than in the former group (i.e. RR 3.9 versus RR 2.0). Chemotherapy treatment itself leads to a significant increase in the risk of lung cancer, lymphomas, leukemias, and pleural cancers, whilst combined therapy leads to not only the same, (excepting the case of pleural cancer), but also to an increased risk of 10 other cancers. Of all chemotherapy schemes, the lowest risk of developing secondary cancer was observed for ABVD (i.e. adriamycin, bleomycin, vinblastine, dacarbazine). The study also showed that differences in cancer risk depended on the patient's age at start of treatment.

Breast and lung cancer are the most commonly found solid tumours post-treatment in HL patients. Breast cancer usually occurs within 10–15 years after the end of therapy [5]. The main risk factor is irradiation at a young age, and it depends on the dose received by the breast [25] and the type of the irradiation field [24, 26]. Premature menopause exerts a protective effect. HL patients after RT treatment have a greater risk of developing metachronous and synchronous contralateral breast cancer [27]. A useful screening test, even in young patients, is mammography (MMG) [5]. Mammography should be recommended no later than 8–10 years after therapy is completed, or from the age of 40 years in patients that received irradiation of the chest or axillary vein regions [2, 5]. A prospective trial comparing the efficacy of MMG and magnetic resonance imaging (MRI) for detecting breast cancer in patients receiving mantle field radiation aged below 35 years showed no difference in the sensitivity of both methods [28] (MMG 68% vs. MRI 67%). It becomes higher (94%) when both methods are used. MRI is additionally recommended for women receiving RT around the chest area before the age of 30 years [29].

Risk factors for lung cancer include prior RT, the use of alkylating agents and etoposide as well as smoking [23, 30]. It has been shown that exposure to radiation at doses greater than 5 Gy or treatment with alkylating agents increases the risk of lung cancer by — respectively — 5.9 fold and 4.2 fold, and this risk increases with the irradiation dose and the number of chemotherapy courses. For patients treated with chemotherapy, a significant increase in lung cancer risk was observed in the first four years after end of treatment, whilst for RT this started after five years and was maintained for more than 20 years after treatment. In the case of combined therapy, this risk was eight times higher, whilst smoking additionally increased the risk 20-fold.

Given the poor prognosis for lung cancer, it seems reasonable to optimally perform screening by using low-dose CT in risk-factor patients [31], although there are no strict guidelines as to the timing and schedule for such tests.

Furthermore, leukemias and non-HL occur more frequently in HL patients after treatment. The risk factors are both systemic therapy (above all, regimens including alkylating agents and etoposide) along with RT. A study by Swerdlow [23] showed that the risk of these tumours was greater for combined therapy when chemotherapy contained alkylating agents. However, in a study comparing escalated dose BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) with primary BEACOPP and COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) alternating with ABVD [32], higher rates of acute myelogenous leukemias (AML) and myelodysplastic syndromes (MDS) were observed in the escalated dose BEACOPP group (respectively, 3% vs. 1.5% vs. 0.4%); nonetheless, the total number of secondary tumours did not differ between arms. Importantly, almost all cases of AML/MDS occurred in the first seven years of follow-up, and the majority (64%, i.e. 9 out of 14) within the first five years.

Monitoring non-cancerous complications of therapy

Cardiovascular disease

There is an increased likelihood of cardiovascular disease and death resulting from patients treated for HL [5, 33]. The main risk factors are mediastinal radiotherapy and anthracyclin-containing chemotherapy [2, 34]. A variety of disorders were seen in patients also previously asymptomatic, for instance coronary artery disease, cardiomyopathy, valvular damage, changes in the pericardium, or cardiac arrhythmias [35]. Symptoms can occur at any time and in the case of RT, usually 5–10 years after treatment. A study of 1474 patients [34] demonstrated that patients after HL treatment have a 3–5 times higher risk of serious cardiovascular disease compared to the general population. However, a study evaluating changes in coronary arteries in asymptomatic patients during first 5 years after treatment found abnormalities in 15% of patients, with significant increases in subsequent years of observation, in which they appeared 15 years after the end of treatment in up to 35% of patients [36]. A multivariate analysis revealed that the risk factors were age during treatment, hypertension, hypercholesterolaemia, and — above all — radiotherapy dose exposed by coronary

arteries. Such an impact of radiation dose (as one of the most important risk factors for heart damage and death thereby arising) has also been demonstrated in many other studies [37, 38]. A prospective study evaluating asymptomatic patients after mediastinal radiation therapy, who received at least 35 Gy, found ommonly valve lesion changes that mainly occurred in the aortic valve (most often regurgitation and stenosis of the mitral, aortic, and tricuspid valves) [39]. The rates of these abnormalities significantly increased over the time of observation, where the number of echocardiograms required to qualify one candidate for endocarditis prevention in patients up to 10 years after treatment was 13, for those treated 11–20 years ago this was 4, and for those treated over 20 ago this was 1.6. Such results confirm the validity of performing echocardiograms, particularly in patients irradiated more than 10 years earlier, although indications must be individualised, and that there are no data regarding frequency of such procedures.

The same study group investigated similar patients that had undergone mediastinal irradiation and identified those that required further diagnostic and intervention treatment for coronary artery disease based on exercise stress tests of echocardiography and myocardial perfusion imaging [40]. For those patients with abnormalities, coronary angiograms were performed, of whom 55% had coronary artery stenosis by over 50%, 22.5% had less than 50%, and 22.5% showed no change. The data thus confirm that testing of asymptomatic patients following mediastinal radiotherapy is appropriate. In those receiving RT of the neck, an increased risk was observed. Another study found that this risk was 4-fold higher when patients were treated at childhood [41], for whom a predisposing factor was having undergone mantle field radiation, possibly as a result of damage to the carotid artery and vein disorders. A further study [38] confirmed that subclavian artery stenosis depended on the RT dose applied to the neck area.

Radiation therapy is not the only cause of increased rates of cardiovascular disease. A recent assessment of cardiovascular disease risk after HL treatment [42] also confirmed the adverse effects of anthracycline-based chemotherapy, showing a 1.5-fold increased risk of valve damage and a 3-fold increased risk of congestive heart failure. Here also, the adverse effects of mediastinal radiotherapy were demonstrated, which increased the risk of coronary heart disease by 2.7 times, valvular disease by 6.6 times, and congestive heart failure by 2.7 times. When both treatments were used, such adverse effects became cumulative. The greatest risk was in patients aged below 25 years, and it lasted more than 35 years after treatment had ended.

The role of classical but modifiable risk factors for cardiovascular diseases was also noted, such as hypercholesterolaemia, hypertension, and smoking [38, 43]. There is evidence suggesting that measuring the lipid profile every three years and introducing statin therapy to these patients can reduce the number of cardiac deaths. When introducing such preventative measures, other risk factors for cardiovascular disease should also be considered and modified accordingly [44].

Thyroid disease

Thyroid problems affect approximately 50% of patients receiving radiotherapy in the neck or upper mediastinum areas [2, 45]. The vast majority (90%) are hypothyroidism cases, of which around half have a subclinical course. They most commonly happen up to 5 years post-treatment, although the increased risk persists for more than 20 years after finishing therapy with additional risk factors of older age, female gender, and higher dose of radiation [46]. Other disorders, like Graves-Basedova disease, are also far more frequent in this group of patients. The much higher risk of thyroid cancer [22, 45] should not be forgotten, which appears more often in patients irradiated at a young age.

Lung disease

The two main risk factors for lung damage are RT and the use of bleomycin. Acute radiation pneumonitis affects 3–10% of patients following mediastinal irradiation [5, 47]. A prospective study [48] evaluating lung function during and within one year of ending treatment (regimens containing bleomycin and some including additional irradiation) [48] found that 12% patients had symptomatic pulmonary toxicity associated with bleomycin (a predisposing factor was older age) and 13% developed irradiated radiation pneumonitis. Impaired lung function (assessed as a change in diffusing capacity) was observed in 35% of patients after 6 months and 25% after 12 months; with most of these patients being asymptomatic. In the case of chemotherapy alone, the lung diffusing capacity was significantly reduced after a month following treatment, but then returned to normal at after 6 months of follow-up. Supplementing with RT had no significant effect on any further decrease, nevertheless the reduced diffusing capacity was maintained a year after treatment. The risk factors were RT dose, the irradiated lung volume, and smoking cigarettes.

There is some evidence suggesting that the use of granulocyte colony stimulating factors (G-CSF), enhances pulmonary toxicity induced by bleomycin. This was found significantly more often in patients treated with G-CSF (26% vs. 9%), and its incidence was associated with a reduced 5-year survival (63% vs. 90%). The

risk factor was age above 40 years [49]. These findings indicate caution when using growth factors during chemotherapy with bleomycin; the more that has been demonstrated that patients undergoing chemotherapy according to the ABVD regimen, can be safely treated with appropriate dosing without using G-CSF, despite neutropenia and even agranulocytosis, at the time the next cycle is scheduled [50, 51].

The risk of pneumotoxicity requires avoidance of bleomycin with brentuximab vedotin (BV) in combination [52] (the same applies to combinations of BV and gemcitabine or RT).

In order to reduce pulmonary complications linked to bleomycin, attempts have been made to avoid using this drug in chemotherapy protocols. Findings have shown that in those patients with advanced disease and treated with escalated BEACOPP, bleomycin can be omitted after 4 cycles of chemotherapy without affecting the efficacy of treatment [53]. Similar conclusions were drawn from advanced HL patients treated with the ABVD regimen. In patients with negative interim PET after 2nd ABVD cycle, bleomycin can be omitted in the next 4 cycles without reduction in the treatment efficacy. However, in patients with early HL (without risk factors) and treated with 2 cycles of ABVD and inverted field radiotherapy (IFRT), omitting bleomycin reduced the effectiveness of treatment [55].

Pulmonary fibrosis, as a late complication, is a significant risk factor for chronic fatigue syndrome and for significant deterioration in the quality of life of patients after HL treatment [56].

Impaired gonadal function

The risk of permanent damage to the gonads is primarily associated with aggressive chemotherapy or RT. The most widely used regimen is ABVD, which now appears to have no adverse effect on fertility [57, 58]. In contrast, the use of escalated BEACOPP, when compared to other chemotherapy regimens, shows a substantial risk of amenorrhea in women [59] and towards the most vulnerable treated patients, consisting of women with advanced disease, being over 30 years age, and those who are not using oral contraception during chemotherapy. In men, the BEACOPP protocol used in both basic and escalated doses results in nearly 90% azoospermia; however, it should be noted that up to 77% of patients were already diagnosed with dyspermia when advanced HL had been diagnosed [60]. Most patients also demonstrated abnormal hormone levels after treatment; 93% for follicle-stimulating hormone (FSH), 21% for luteinising hormone (LH), and 57% for testosterone. This was independent of the type of BEACOPP applied.

Neuropathy

Neuropathy is a common side effect of the "vinca rosea" alkaloid (a chemotherapeutic agent; vincristine), with other undoubted risk factors being older age and comorbidities like diabetes. Complications above grade 3 are rare, and in ABVD chemotherapy, sensory neuropathy was seen in around 3% of patients, and locomotory neuropathy in 2% of patients [61]; in those aged over 60 years the corresponding rates were 12% and 8%, respectively [62]. If neurotoxicity occurs in patients with advanced disease treated with escalated BEACOPP, then there is evidence showing that discontinuing vincristine at the fourth course of chemotherapy may not affect the efficacy of treatment [53].

Peripheral neuropathy is also caused by BV. Sensory complications often occur in around 42–74% of patients [63–65], and rates depend on age, comorbidities, a history of earlier treatment, and the duration of current therapy. Serious complications from grade 3 are seen in 8–15% of patients. Locomotory neuropathy symptoms are rare; however, they are significant and can affect up to 23% of patients [66]. Extending intervals between chemotherapy cycles and reducing doses usually permit treatment to be continued without any serious consequences.

Other complications

Patients who require auto- or allotransplantation of haematopoietic stem cells, as well as RT, have an increased risk of infection due to immunosuppression. Chronic fatigue syndrome should also not be ignored, which affects both mental and physical well-being [56], as well as being a factor in evaluating the quality of life and returning back to social, family, and professional functioning.

Recommendations for early and late monitoring of patients after treatment

Because precise guidelines are lacking, along with any high quality evidence on HL patients follow-up, medical practice relies mainly on the practical experience accrued within centres/institutes and that of doctors. According to our presented study, post-HL treatment differences in follow-up between various Polish centres are significant. In some measure, however, the frequency of patient monitoring visits and the type of tests performed depends on many factors such as age, disease severity, type of applied therapy, the results of PET/CT during treatment, and the reported symptoms. Nevertheless, Hodgkin Lymphoma Section of the Polish Lymphoma Research Group have prepared re-

commendations [based on 1, 2, 67, 68] for the follow-up procedures of asymptomatic patients that may be helpful in everyday clinical practice. These are shown below. If any symptoms do appear, then this would naturally require a separate procedure.

1. Performing PET/CT at the end of treatment (within 4–6 weeks after chemotherapy and 3 months after combined treatment with RT) in order to confirm metabolic remission (scores 1, 2, 3 according to the Deauville scale).
2. Monitoring visits made every 3 months for the first year, every 4 months during the second year, every 6 months in the third year, and thereafter once annually for the rest of life. Each visit requires:
   a. a physical examination;
   b. teaching patients about possible signs of recurrence, complications/side effects of treatment, a healthy lifestyle, and breast self-examination for women;
   c. assessing the quality of life and psycho-social function.
3. Laboratory tests:
   a. at each visit measuring; morphology, ESR, CRP, and LDH;
   b. other biochemical tests deemed necessary by the doctor;
   c. measuring TSH (thyroid-stimulating hormone) once a year in patients who received RT to the neck or upper mediastinum;
   d. measuring sex hormones and sperm is recommended in younger patients wanting to have children after treatment, especially those treated with aggressive chemotherapy or RT in the gonadal regions;
   e. a lipid profile every 2–3 years, and 5 years, after finishing therapy, particularly in patients at risk of cardiovascular disease.
4. Imaging tests in asymptomatic patients for detecting recurrence is not recommended. The only possible exception being patients bearing risk factors for rapid recurrence and where a PET/CT may be performed after 6 months from the PET/CT performed at the end of treatment. Such risk factors are as follows:
   a. early PET/CT outcome scoring positive (i.e. Deauville 4 and 5 score); recommended after 2 cycles of chemotherapy;
   b. the residual uptake (Deauville 3 score) in PET/CT after treatment;
   c. localised primary extra-nodal involvement (particularly the bone marrow, bone, and lung).
5. Measuring blood pressure at each visit, performing echocardiography after treatment and then again after 5 years and a carotid ultrasound after 10 years in patients at risk from cardiovascular disease.
6. A low-dose chest CT/X-ray after 5 years, (for patients treated with alkylating agents after 3 years), particularly in groups at risk of lung cancer (e.g. those smoking cigarettes).
7. Performing MMG, ultrasound, or breast MRI imaging (MRI especially in patients irradiated before 30 years age), 8–10 years after treatment, or from 40 years age in patients undergoing RT to the chest or armpit.
8. Colonoscopy every 10 years; the first should be considered at ages 40 years and above.
9. Annual influenza vaccination.
10. Recommended meningococcal, pneumococcal, and Haemophilus influenzae vaccinations every 5 years in patients after splenectomy or those undergoing RT that includes the spleen region.

References

1. Wróbel T, Chłoniak Hodgkina. In: Krzakowski M, Potemski P, Warzocha K, Wysocki P (ed). Onkologia Kliniczna, t. III, 2015: 1423.
2. NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, Version 2.2015, dostępne na www.nccn.org.
3. Radford JA, Eardley A, Woodman C, Crowther D. Follow up policy after treatment for Hodgkin disease: too many clinic visits and routine tests? A review of hospital records. BMJ 1997; 314: 343–346.
4. Torrey MJ, Poen JC, Hoppe RT. Detection of relapse in early-stage Hodgkin disease: role of routine follow-up studies. J Clin Oncol 1997; 15: 1123–1130.
5. Ha CS, Hodgson DC, Advani R et al. ACR appropriateness criteria follow-up of Hodgkin lymphoma. J Am Coll Radiol 2014; 11 (11): 1026–1033.
6. Dryver ET, Jernstrom H, Tompkins K, Buckstein R, Imrie KR. Follow-up of patients with Hodgkin disease following curative treatment: the routine CT scan is of little value. Br J Cancer 2003; 89: 482–486.
7. Xavier MF, Schuster SJ, Andreadis C et al. Detection of relapse in diffuse large B-cell lymphoma (DLBCL) and Hodgkin's lymphoma (HL): observations andimplications for post-remission radiologic surveillance. ASH Ann Meet Abstr 2006; 108: 2428.
8. Zinzani PL, Stefoni V, Tani M et al. Role of [18F] fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol 2009; 27: 1781–1787.
9. Mocikova H, Obrtlikova P, Vackova B, Trneny M. Positron emission tomography at the end of first-line therapy and during follow-up in patients with Hodgkin lymphoma: a retrospective study. Ann Oncol 2010; 21 (6): 1222–1227.
10. El-Galaly TC, Mylam KJ, Brown P et al. PET/CT surveillance in patients with Hodgkin lymphoma in first remission has a low positive predictive value and high costs. Haematologica 2012; 97: 931–936.
11. Lee AI, Zuckerman DS, Van den Abbeele AD et al. Surveillance imaging of Hodgkin lymphoma patients in first remission: a clinical and economic analysis. Cancer 2010; 116: 3835–3842.
12. Maeda LS, Horning SJ, Iagaru AH et al. Role of FDG-PET/CT Surveillance for Patients with Classical Hodgkin's Disease in First Complete Response: The Stanford University Experience. ASH Ann Meet Abstr 2009; 114: 1563.
13. Petrausch U, Samaras P, Veit-Haibach P et al. Hodgkin's lymphoma in remission after first-line therapy: which patients need FDG-PET/CT for follow-up? Ann Oncol 2010; 21: 1053–1057.
14. Basciano BA, Moskowitz C, Zelenetz AD. Impact of routine surveillance imaging on the outcome of patients with relapsed Hodgkin lymphoma. ASH Ann Meet Abstr 2009; 114: 1558.
15. Friedmann AM, Wolfson JA, Hudson MM et al. Relapse after treatment of pediatric Hodgkin lymphoma: outcome and role of surveillance after end of therapy. Pediatr Blood Cancer 2013; 60: 1458–1463.
16. Voss SD, Chen L, Constine LS et al. Surveillance computed tomography imaging and detection of relapse in intermediate- and advanced-stage pediatric Hodgkin's lymphoma: a report from the Children's Oncology Group. J Clin Oncol 2012; 20; 30: 2635–2640.

17. Dann EJ, Berkahn L, Mashiach T et al. Hodgkin lymphoma patients in first remission: routine positron emission tomography/computerized tomography imaging is not superior to clinical follow-up for patients with no residual mass. Br J Haematol 2014; 164 (5): 694–700.
18. Picardi M, Pugliese N, Cirillo M et al. Advanced-stage Hodgkin lymphoma: US/chest radiography for detection of relapse in patients in first complete remission — a randomized trial of routine surveillance imaging procedures. Radiology 2014; 272 (1): 262.
19. Cardis E, Vrijheid M, Blettner M et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. Radiat Res 2007; 167 (4); 396–416.
20. Crowley MP, O'Neill SB, O'Neill DC et al. Radiation Exposure From Diagnostic Imaging in Patients with Lymphoma — The Cost Of The Cure? 55th ASH annual Meeting 2013, Abstract 557 from session 901: Health Services and Outcomes Research: Survivorship and Standardization of Care.
21. Aleman BM, van den Belt-Dusebout AW, Klokman WJ et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003; 21: 3431–3439.
22. 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: 1489–1497.
23. 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: 4096–4104.
24. Franklin J, Pluetschow A, Paus M et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trias. Ann Oncol 2006; 17: 1749–1760.
25. 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: 971–980.
26. 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: 4239–4246.
27. Elkin EB, Klem ML, Gonzales AM 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. J Clin Oncol 2011; 29: 2466–2473.
28. Ng AK, Garber JE, Diller LR et al. Prospective study of the efficacy of breast MRI and mammographic screening in survivors of Hodgkin lymphoma. J Clin Oncol 2013; 31: 2282–2288.
29. Saslow D, Boetes C, Burke W et al.; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007; 57 (2): 75–89.
30. Travis LB, Gospodarowicz M, Curtis RE et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002; 94: 182–192.
31. Das P, Ng AK, Earle CC, Mauch PM, Kuntz KM. Computed tomography screening for lung cancer in Hodgkin's lymphoma survivors: decision analysis and cost-effectiveness analysis. Ann Oncol 2006; 17: 785–793.
32. Engert A, Diehl V, Franklin J et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol 2009; 27: 4548–4554.
33. Ng AK, Bernardo MV, Weller E et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. Blood 2002; 100: 1989–1996.
34. 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.
35. Carver JR, Shapiro CL, Ng A et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol 2007; 25: 3991–4008.
36. Girinsky T, M'Kacher R, Lessard N et al. Prospective Coronary Heart Disease Screening in Asymptomatic Hodgkin Lymphoma Patients Using Coronary Computed Tomography Angiography: Results and Risk Factor Analysis. IJROBP 2014; 89, 1: 59–66.
37. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA 1993; 270: 1949–1955.
38. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA 2003; 290: 2831–2837.
39. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol 2003; 42: 743–749.
40. Heidenreich PA, Schnittger I, Strauss HW et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. J Clin Oncol 2007; 25: 43–49.
41. Bowers DC, McNeil DE, Liu Y et al. Stroke as a late treatment effect of Hodgkin's Disease: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2005; 23 (27): 6508–6515.
42. Van Nimwegen FA, Schaapveld M, Janus CP et al. Cardiovascular Disease After Hodgkin Lymphoma Treatment: 40-Year Disease Risk. JAMA Int Med 2015; 27. doi: 10.1001/jamainternmed.2015.1180.
43. Glanzmann C, Huguenin P, Lutolf UM, Maire R, Jenni R, Gumppenberg V. Cardiac lesions after mediastinal irradiation for Hodgkin's disease. Radiother Oncol 1994; 30: 43–54.
44. Chen AB, Punglia RS, Kuntz KM, Mauch PM, Ng AK. Cost effectiveness and screening interval of lipid screening in Hodgkin's lymphoma survivors. J Clin Oncol 2009; 27: 5383–5389.
45. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991; 325: 599–605.
46. Sklar C, Whitton J, Mertens A et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2000; 85: 3227–3232.
47. Koh ES, Sun A, Tran TH et al. Clinical dose-volume histogram analysis in predicting radiation pneumonitis in Hodgkin's lymphoma. IJROBP 2006; 66: 223–228.
48. Ng AK, Li S, Neuberg D et al. A prospective study of pulmonary function in Hodgkin's lymphoma patients. Ann Oncol 2008; 19: 1754–1758.
49. Martin WG, Ristow KM, Habermann TM et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol 2005; 23 (30): 7614–7620.
50. Evens AM, Cilley J, Ortiz T et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 2007; 137 (6): 545–552.
51. Boleti E, Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. Ann Oncol 2007; 18 (2): 376–380.
52. Younes A, Connors JM, Park SI et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. Lancet Oncol 2013; 14 (13): 1348–1356.
53. Haverkamp H, Böll B, Eichenauer DA et al. Impact of Bleomycin and Vincristine Dose Reductions in Patients With Advanced Hodgkin Lymphoma Treated With BEACOPP: An Analysis of the German Hodgkin Study Group HD12 and HD15 Trials. J Clin Oncol 2015; 33 (22): 2430–2436.
54. Johnson PW, Federico M, Fossa A et al. Response rates and toxicity of response-adapted therapy in advanced Hodgkin lymphoma: Initial results from the International RATHL Study. Haematologica 2013; 98: 2.
55. Behringer K, Goergen H, Hitz F et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. Lancet 2015; 385 (9976): 1418–1427.
56. Knobel H, Havard Loge J, Lund MB, Forfang K, Nome O, Kaasa S. Late medical complications and fatigue in Hodgkin's disease survivors. J Clin Oncol 2001; 19: 3226–3233.
57. Hodgson DC, Pintilie M, Gitterman L et al. Fertility among female Hodgkin lymphoma survivors attempting pregnancy following ABVD chemotherapy. Hematol Oncol 2007; 25: 11–15.
58. Kulkarni SS, Sastry PS, Saikia TK, Parikh PM, Gopal R, Advani SH. Gonadal function following ABVD therapy for Hodgkin's disease. Am J Clin Oncol 1997; 20: 354–357.
59. Behringer K, Breuer K, Reineke T 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. J Clin Oncol 2005; 23: 7555–7564.
60. Sieniawski M, Reineke T, Nogova L et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG). Blood 2008; 111: 71–76.
61. Gordon LI, Hong F, Fisher RI et al. Randomized Phase III Trial of ABVD Versus Stanford V With or Without Radiation Therapy in Locally Extensive and Advanced Stage Hodgkin Lymphoma: An Intergroup Study Coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol 2013; 31 (6): 684–691.
62. Evens AM, Hong F, Gordon LI et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older

Hodgkin lymphoma patients: a comprehensive analysis from the North American intergroup trial E2496. Br J Haematol 2013; 161 (1):76–86.
63. Younes A, Gopal AK, Smith SE et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012; 30 (18): 2183–2189.
64. Gopal AK, Bartlett NL, Forero-Torres A et al. Brentuximab vedotin in patients aged 60 years or older with relapsed or refractory CD30-positive lymphomas: a retrospective evaluation of safety and efficacy. Leuk Lymphoma 2014; 55 (10): 2328–2334.
65. Forero-Torres A, Bartlett NL, Berryman RB et al. Extended treatment with brentuximab vedotin in patients with relapsed or refractory CD30-positive hematological malignancies. Leuk. Lymphoma 2015; 56 (4): 1151–1153.
66. Moskowitz CH, Nademanee A, Masszi T et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015; 385 (9980): 1853–1862.
67. Wróbel T, Chłoniak Hodgkina. In: Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych 2013 rok. Onkol Prakt Klin 2013; 9 (suppl B): 989.
68. Eichenauer DA, Engert A, André M et al.; on behalf of the ESMO Guidelines Working Group . Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (suppl 3): iii70–iii75.