22 Late Effects After Treatment of Hodgkin Lymphoma in Childhood and Adolescence

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22.1 Treatment for Hodgkin Lymphoma in Childhood and Adolescence

Pediatric Hodgkin lymphoma (HL) has now been treated successfully in cooperative group trials [1–5] since the late 1970s. In adult patients with early-stage disease, high-dose extended field radiation was shown to be effective. Chemotherapy combinations of mechlorethamine, vincristine, procarbazine and prednisone as well as doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or combined-modality treatment were only given for advanced disease [6]. For children, these treatments were modified by reducing radiotherapy and field size and applying chemotherapy across all disease stages. When concerns about late effects of treatment in aging survivors of pediatric cancer emerged [7–10], general treatment approaches started to change. The use of alkylators was reduced, and the number and composition of chemotherapy cycles were adapted to individual risk factors [2–4, 11, 12]. Radiotherapy (RT) was limited to involved fields and doses adapted to disease risk [1–4]. Furthermore, the concept of tailoring therapy in dose-dense regimens by using early response assessment was refined [12]. Procarbazine was gradually eliminated to reduce the risk of male infertility; etoposide and doxorubicine were substituted to reduce the cumulative alkylating dose [12–15]. Varied treatment approaches for pediatric HL have evolved by collaboration among cooperative groups. Most European and North American study groups have pursued combined-modality treatment approaches [4, 14, 16–25]. Central and South American groups however used to favor chemotherapy-only regimes [26, 27].

22.1.1 Evolution of Treatment by Consecutive Trials

The most recent European trial builds on the experience from eight successive DAL/GPOH study generations starting the first trial in 1978. Treatment of pediatric Hodgkin's lymphoma has stepwise been optimized since and established the current standard in the participating countries. From the second study generation (DAL-HD-82) onward, the backbone of the treatment strategy has been constituted, and changes have evolved gradually.

Patients have been stratified into three treatment groups (TG-1, TG-2, and TG-3) according to Ann Arbor stage (TG-1 stage IA/B and IIA; TG-2 stage IEA/B, IIEA, IIB, and IIA; TG-3 stage IIEB, IIIEA/B, IIIB, and IVA/B). All patients started treatment with two intensive

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induction chemotherapy cycles. Initially, the OPPA cycle comprised the standard treatment for induction, and later the OEPA cycle was used.

Patients in TG-2 and TG-3 received two and four chemotherapy cycles for consolidation, respectively. The COPP cycle comprised the standard consolidation treatment, and the COPDAC cycle was used later.

Following chemotherapy, all patients used to receive involved field radiotherapy (RT). Then involved-node RT was administered in selected cases only and based on response assessment. For details and treatment evolution over 30 years from DAL-HD 78 up to GPOH- HD 2002, see Table 22.1.

22.1.2 Elimination of Procarbazine and Introduction of Dose-Dense Chemotherapy Regimen to Preserve Male Fertility

After it became apparent that procarbazine induces male infertility [28], several attempts were made to eliminate procarbazine from the OPPA (vincristine, procarbazine, prednisone, doxorubicin) and COPP (cyclophosphamide, vincristine, procarbazine, prednisone) cycle in order to reduce male infertility and preserve high cure rates.

In the DAL-HD 85 study, procarbazine was omitted in OPA (vincristine, prednisone, doxorubicin) and replaced by methotrexate in COMP (cyclophosphamide, vincristine, methotrexate, prednisone). By eliminating procarbazine, male fertility indeed was preserved [28, 29], but treatment efficacy was compromised with 4-year EFS rate dropping to 54–86% [30]. In the following study generation DAL-HD 87, procarbazine was reintroduced into the COPP cycle but still omitted in the OPA cycle. 7-year EFS and overall survival (OS) rates for all patients improved (85% and 97%, respectively) [31] but still were lower than in the previous DAL-HD 82 study generation. Induction treatment was therefore re-intensified in the following DAL-HD 90 study: female patients received again OPPA cycles; in male patients, procarbazine was replaced by 500 mg/m^2 etoposide given over 4 days (OEPA) [4]. With this strategy, EFS rate and OS improved again to results comparable to the previous DAL-HD 82 study although therapy intensity was clearly reduced. By introducing etoposide, the rate of male infertility was significantly reduced [32] in TG-1 (2× OEPA), while about half of the male patients in TG-2 and TG-3 still showed abnormal FSH values after 2× or 4× COPP cycles. There was however a tendency for worse EFS in male patients compared to female patients. Based on the assumption that OEPA was less effective than OPPA, OEPA was intensified extending etoposide administration from 4 to 5 days (OE*PA with 20% more etoposide). Furthermore procarbazine was replaced by dacarbazine in the COPP cycle resulting in COPDAC (cyclophosphamide, vincristine, dacarbazine, prednisone) as procarbazine could not be dropped without being replaced by an appropriate substitute. Dacarbazine is less likely to cause infertility in males and a premature menopause in females. In the following HD 2002 pilot study, all male patients received a completely procarbazine-free regimen with intensified OE*PA and COPDAC cycles. Outcomes of male patients treated with the OEPA-COPDAC regimen were comparable to those of female patients receiving the OPPA-COPP standard treatment [14]. In contrast to these gender-stratified trials, the effect of OE*PA-COPDAC versus OE*PA-COPP was the subject of the following EuroNET-PHL-C1 trial. All patients now received OE*PA, but patients in intermediate- (TG-2) and high-risk (TG-3) groups were randomized to receive either COPP or COPDAC.

22.1.3 Response Adaptation to Reduce or Eliminate RT

In HL trials in adults, RT remains an essential component of treatment, especially for patients with early-stage disease who are treated with ABVD chemotherapy. The combined-modality approaches provide high response rates with EFS rates of 90%, but the risk of radiation-induced late effects such as

Table 22.1 Evolution of pediatric Hodgkin lymphoma treatment over 30 years from DAL-HD 78 up to GPOH-HD 2002

Trial	Patients (n)	Splenectomy for staging	Chemotherapy	Indication for RT	Radiotherapy: Standard dose (Gy) and field			EFS	OS
					TG 1	TG 2	TG 3		
DAL-HD 78 1978–1981	170	91%	TG 1 (I, IIA): 2× OPPA[a] TG 2 (> IIA): 2× OPPA[a], 4× COPP[a] VBL during RT	All patients	36–40 EF/36–40 IF and 18–20 to adjacent fields			87% [30]	92%
DAL-HD 82 1982–1984	203	40%	TG 1 (I, IIA): 2× OPPA[a] TG 2 (IIB, IIIA): 2× OPPA[a], 2× COPP[a] TG 3 (IIIB, IV): 2× OPPA[a], 4× COPP[a]	All patients	35 IF	30 IF 5–0[a]	25 IF 5–10[a]	94% [30]	95% [30]
DAL-HD 85 1985–1986	98	32%	TG 1 (I, IIA): 2× OPA TG 2 (IIB, IIIA): 2× OPA, 2× COMP TG 3 (IIIB, IV): 2× OPA, 4× COMP	All patients	35 IF	30 IF 5–10[a]	25 IF 5–10[a]	72% [30]	99% [30]
DAL-HD 87 1987–1990	196	30%	TG 1 (I, IIA): 2× OPA TG 2 (IIB, IIIA): 2× OPA, 2× COPP[b] TG 3 (IIIB, IV): 2× OPPA[b], 4× COPP[b]	All patients	30 IF	25 IF 5–10[a]	20 IF 5–10[a]	85% [31]	97% [31]
DAL-HD 90 1990–1995	574	–	TG 1 (I, IIA): girls: 2× OPPA[b], boys: 2× OEPA TG 2 (IE, IIB, IIEA, IIIA): girls: 2× OPPA[b], 2× COPP[c], boys: 2× OEPA, 2× COPP[c] TG 3 (IIEB, IIIB, IIIEA, IV): girls: 2× OPPA[b], 4× COPP[c], boys: 2× OEPA, 4× COPP[c]	All patients	25 IF 5–10[a]	25 IF 5–10[a]	20 IF 10–15[a]	91% [4]	98% [4]
GPOH-HD 95 1995–2001	925	–	TG 1(I, IIA): girls: 2× OPPA[b], boys: 2× OEPA TG 2(IE, IIB, IIEA, IIIA): girls: 2× OPPA[b], 2× COPP[c], boys: 2× OEPA, 2× COPP[c] TG 3 (IIEB, IIIB, IIIEA, IV): girls: 2× OPPA[b], 4× COPP[c], boys: 2× OEPA, 4× COPP[c]	All patients except for CR at end of chemotherapy	20 mIF 10–15[a]	20 mIF 10–15[a]	20 mIF 10–15[a]	88% [21]	97% [21]
GPOH-HD 2002 2002–2005	573	–	TG 1(I, IIA): girls: 2× OPPA[b], boys: 2× OE*PA TG 2(IE, IIB, IIEA, IIIA): girls: 2× OPPA[b], 2× COPP[c], boys: 2× OE*PA, 2× COPDAC TG 3 (IIEB, IIIB, IIIEA, IV): girls: 2× OPPA[b], 4× COPP[c], boys: 2× OE*PA, 4× COPDAC	All patients except for CR in TG-1	20 mIF 10–15[a]	20 mIF 10–15[a]	20 mIF 10–15[a]	98% [14]	97% [14]

Abbreviations: *CR* complete remission (≥95% reduction of initial nodal volume and ≤2 mL residual volume in any initially involved site), *EF* extended field, *EFS* event-free survival, *IF* involved field, *mIF* modified involved field, *OS* overall survival, *PET* positron emission tomography, *RT* radiotherapy, *TG 1* treatment group 1, *TG 2* treatment group 2, *TG 3* treatment group 3

[a]Boost: if <75% volume reduction or <50 mL (DAL-HD 95) or >100 mL (GPOH-HD 2002, EuroNet-PHL-C1) residual mass in any initially involved nodal site

(continued)

Table 22.1 (continued)

[b]Modified involved field: lateral margins of radiation field depend on the residual tumor extension at end of chemotherapy

Cumulative doses per cycle:

OPPA[a]: prednisone (900 mg/m^2), procarbazine (1500 mg/m^2) max. daily dose 150 mg; vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

OPA: prednisone (900 mg/m^2), vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

OPPA[b]: prednisone (900 mg/m^2), procarbazine (1500 mg/m^2), vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

OEPA: prednisone (900 mg/m^2), etoposide (500 mg/m^2), vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

OE*PA: prednisone (900 mg/m^2), etoposide (625 mg/m^2), vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

COPP[a]: prednisone (560 mg/m^2) only in 2. and 4. cycle, procarbazine (1400 mg/m^2) max. daily dose 150 mg, vincristine (3 mg/m^2) max. single dose 2 mg cyclophosphamide (1000 mg/m^2)

COMP: prednisone (560 mg/m^2) only in 2. and 4. cycle, methotrexate (80 mg/m^2), vincristine (3 mg/m^2) max. single dose 2 mg, cyclophosphamide (1000 mg/m^2)

COPP[b]: prednisone (560 mg/m^2), procarbazine 1500mg/m^2), vincristine 3 mg/m^2) max. single dose 2 mg, cyclophosphamide (1000 mg/m^2)

COPP[c]: prednisone (600 mg/m^2), procarbazine (1500 mg/m^2), vincristine (3 mg/m^2) max. single dose 2 mg, cyclophosphamide (1000 mg/m^2)

COPDAC: prednisone (600 mg/m^2), dacarbazine (750 mg/m^2), vincristine (3 mg/m^2) max. single dose 2 mg, cyclophosphamide (1000 mg/m^2)

VBL: Vinblastine 2 mg/m^2 every 2 weeks during RT (only if duration of RT is <8 weeks, starting at week 9 of RT)

secondary malignancies, cardiovascular disease, and thyroid dysfunction in survivors after pediatric HL increases throughout their lifetime [9, 10, 33–35]. Pediatric HL study groups therefore balance the risk-benefit ration differently.

The DAL/GPOH-HD/EuroNet-PHL study group successfully reduced RT over eight consecutive trials. For the development of RT regimen by systematic radiotherapy reduction and elimination strategies in the DAL/GPOH-HD/EuroNet-PHL trials, see Table 22.1.

In the GPOH-HD 95 trial, RT was omitted for the first time in patients achieving anatomic CR after OEPA-COPP chemotherapy. In contrast to patients with low-risk disease, patients with intermediate- and advanced-stage disease and CR showed a significantly lower 10-year progression-free survival (PFS) than patients who did not achieved CR and therefore received IFRT [21]. In conclusion, assessment by anatomic response at completion of chemotherapy was not adequate to identify patients in whom RT can be spared without increasing the risk of relapse. In the following EuroNet-PHL-C1 study, RT was omitted in patients whose PET scans were negative after two initial intensified OE*PA cycles. Preliminary data suggest that this strategy is feasible to identify patients to have good long-term survival without RT.

The reader is also referred to the Chaps. 39, 40 of this book.

22.1.4 Standardizing the Definitions for FDG-PET Imaging for Initial Staging and Response Assessment

Functional FDG-PET imaging was increasingly used in Hodgkin's lymphoma already in the 1990s, and it is now routinely used in most centers. FDG-PET can image the entire body detecting peripheral metastatic lesions and more lesions than detected by CT/MRI. It can also better distinguish between vital and fibrotic/necrotic residual masses. This may have impact on disease stage and thus treatment intensity for some patients. FDG-PET images are currently interpreted visually, which is subject to high intraobserver variability [36] and should therefore be centrally reviewed within a clinical trial for quality assurance. FDG-PET-guided response adaption is increasingly used, but evaluation may differ by study groups. For the current EuroNet-PHL C2 trial, the definition for PET response was changed to a higher threshold for PET positivity with the aim to omit RT in more than 50% of all patients. Figure 22.1 shows FDG PET scan at initial staging and response assessment.

22.1.5 New Agents

New drugs have been studied in patients with relapsed of refractory HL and showed so far promising results for brentuximab vedotin and nivolumab [37]. Bretuximab vedotin has already been introduced into first-line-treatment in adults and children with advanced disease [38, 39] with the aim to further reduce the number of patients who require RT. Long-term effect caused by new agents are not yet clear and need to be carefully monitored.

22.2 Late Effects of Treatment of Hodgkin Lymphoma in Childhood and Adolescence

Long-term survivors of pediatric Hodgkin lymphoma are at risk for a wide range of late effects [40], with second malignant neoplasm and cardiovascular diseases being the leading causes of death in these patients [41]. The excess risks remain significantly elevated decades after treatment and are clearly associated with extent of treatment exposures. With adoption of new agents and contemporary treatment techniques in the evolution of HL-treatment, late effect risks need to be further monitored and follow-up recommendations continuously updated.

22.2.1 Second Malignancy

Pediatric HL survivors have an excess risk of a solid second malignancy that is clearly associated with RT and persists after treatment. Cumulative incidence increased up to 23.5% at 30 years

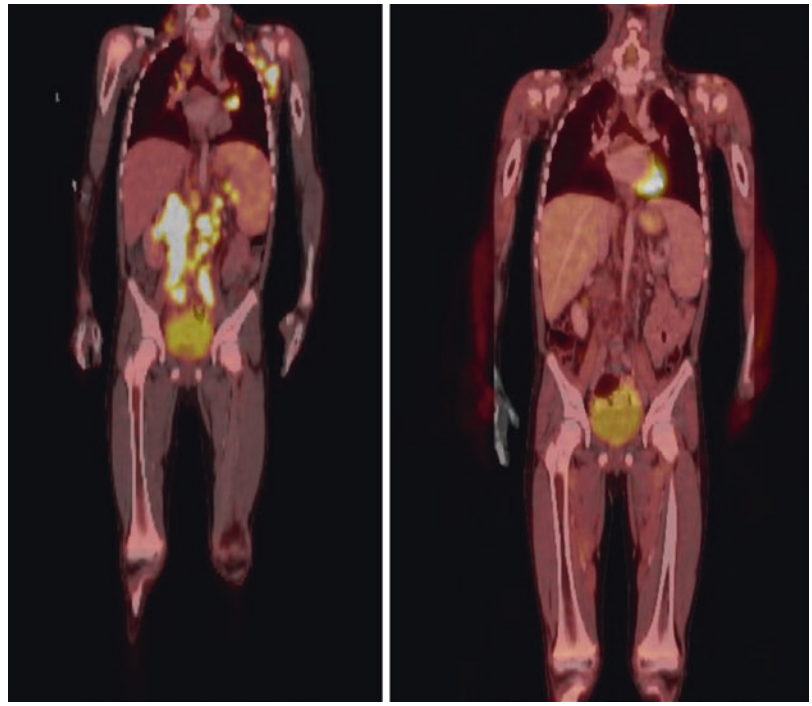

Fig. 22.1 Non-fused (^{18}F)fluoro-deoxy-glucose (FDG) positron emission tomography (PET) images of coronal slices at initial diagnosis (left) and at response assessment (right) after two cycles of OE*PA in a 10-year-old patient with classical Hodgkin lymphoma

[33, 42, 43]. Breast cancer is the most common solid second malignancy followed by thyroid cancer. Other second malignancies include tumors of the bone/connective tissue and esophagus; colorectal, lung, and gastric cancers; and melanoma at a younger age than expected in the general population, necessitating ongoing surveillance of this high-risk population Modern diagnostics, i.e., liquid biopsy, are currently under evaluation and may facilitate screening procedures in the future.

The reader is also referred to Chap. 14 of this book.

22.2.2 Cardiovascular Disease

HL survivors have a significant risk for cardiovascular disease (CVD) [34, 35]; both radiotherapy involving the heart and chemotherapy containing anthracyclines can increase the risk. Radiation-induced CVD includes coronary artery disease, valvular heart disease, myocardial dysfunction, electrical conduction abnormalities, and pericardial disease. Anthracyclines may, depending on the cumulative dose, lead to both acute cardiomyopathy and chronic cardiac conditions, especially congestive heart failure (CHF) [34, 35, 44–46]. Subclinical disease may be frequent, and sudden cardiac death due to silent coronary artery disease has been described [47]. HL survivors aged 50 will experience more than two times the number of chronic cardiovascular health conditions and nearly 5 times the number of more severe cardiovascular conditions compared to the general population. On average, HL survivors at risk have one severe, life-threatening, or fatal cardiovascular condition [48]. HL survivors were 4.4 times and 6.7 times more at risk of ischemic heart disease and cardiomyopathy/heart failure death, respectively, than expected [49]. HL survivors with radiation to the cervical or mantle region may also seem at risk to develop cerebrovascular disease such as premature carotid stenosis, transient ischemic attack, and stroke [50–52].

The reader is also referred to Chap. 1 of this book.

22.2.3 Pulmonary Dysfunction

Radiation to the lung appears to have the most significant impact upon the lung; survivors can

develop chronic pulmonary conditions such as chronic cough, oxygen need, lung fibrosis, and recurrent pneumonia. Compared to their siblings, patients after lung irradiation with 15 to ≤25 Gy have a 6.2–11.0 increased risk to develop lung fibrosis and a 2.9–3.1 increased risk for recurrent pneumonia [53].

The reader is also referred to Chap. 6 of this book.

22.2.4 Endocrinopathies

22.2.4.1 Fertility Impairment

RT and chemotherapy can both have an effect on the fertility of men and women, depending upon RT dose and cumulative dose of chemotherapy. In men, radiation doses of ≤1.2 Gy are associated with a reduced chance of recovery of spermatogenesis. In women treated at age 15–40 years, ovarian doses of 2.5–5 Gy will lead to permanent ovarian failure in 30–40% [54]. The risk for infertility after chemotherapy depends on the cumulative dose of alkylating agents. In men, procarbazine causes a high and dose-related incidence of testicular dysfunction in prepubertal as well as in pubertal boys affecting Leydig cell function and spermatogenesis, mostly resulting in azoospermia [28]. Woman appear to be less affected [55] but are at risk for premature ovarian insufficiency [56, 57].

The reader is also referred to the Chaps. 9, 10, 12 of this book.

22.2.4.2 Thyroid Dysfunction

Long-term risk in pediatric HL survivors to develop hypothyroidism can be 40% or higher after RT to the neck region [40, 58]. The risk of hypothyroidism after RT is dose related. Adult HL patients showed a risk of 70.8% to develop hypothyroidism, if the thyroid gland volume receiving 30 Gy was greater than 62.5% [54].

The reader is also referred to Chap. 8 of this book.

22.2.5 Other Late Effects

Fatigue is common after HL and local atrophy of muscle and connective tissue may occur. An increased risk of diabetes has been described [54]. Patients after splenectomy for staging are at risk for severe infections [59].

22.3 Recommendation for Follow-Up Exams After Treatment of Hodgkin Lymphoma in Childhood and Adolescence

Lifelong regular follow-up exams according to the risk given by the individual treatment are recommended as given in Table 22.2. Recent evidence-based follow-up recommendations by organ at risk can be reviewed at www.ighg.org, at

Table 22.2 Recommendation for risk-adapted follow-up care in long-term survivors after Hodgkin lymphoma in childhood and adolescence

Organ	Risk factor	Start of surveillance	Surveillance modality	Frequency	References
Heart, cardiovascular system	RT to mediastinum and anthracyclines	No later than 2 years after end of treatment	Cardiac exam, blood pressure, ECG, echocardiography, lipid profile	Every 2 years, prior to pregnancy or in the first trimester	[60–62]
	No RT, anthracycline <250 mg/m^2	No later than 2 years after end of treatment	Echocardiography	Every 5 years	
Cerebrovascular system/ subclavian arteries	RT to neck, supraclavicular, chest, mediastinal or mantle region, in particular ≤40 Gy		Neurological exam, examination of diminished pulses or carotid bruits, blood pressure	Annually	[61]

(continued)

Organ	Risk factor	Start of surveillance	Surveillance modality	Frequency	References
Thyroid	RT to neck or supraclavicular region	After end of treatment	Thyroid exam, TSH, fT4	Every 1–2 years	[61, 62][b]
Lung	RT to axilla, chest, mediastinal or mantle region	After end of treatment	Lung function testing Pulmonary exam	5 and 10 year after end of treatment, consider every 2–5 years thereafter	[61, 62][b]
Fertility					
Male	Cyclophosphamide, procarbazine, busulfan, HSCT[a], RT exposing testes	At survivors' request	Semen analysis		[63]
Female	Alkylating agents, cyclophosphamide, procarbazine, RT exposing ovaries	In case of menstrual cycle dysfunction	FSH, estradiol		[56]
Second malignancies					
Thyroid	RT to neck and supraclavicular and mantle region	5 years after radiation	Neck palpation/ ultrasound	Every 1–2 years	[64]
Breast	RT to mediastinum/ chest/axilla	8 years after radiation or at age 25	Clinical exam, MRI/ultrasound/ according to local screening program for familial breast cancer	Annually	[10, 65]
GI tract	RT to abdomen or or abdominopelvic region	5 years after radiation or at age 30	According to local screening program for familial colon cancer (i.e., colonoscopy every 5 years)		[61, 66]
Skin	Any RT	After end of treatment	Dermatological exam of irradiated field(s)	Annually	[61, 62]

Abbreviations: *RT* radiotherapy, *ECG* electrocardiogram, *TSH* thyroid-stimulating hormone, *fT4* free thyroxine, *FSH* follicle-stimulating hormone, *CT* computed tomography, *MRI* magnetic resonance imaging
[a]with conditioning regimen cyclophosphamide or fludarabine and melphalan
[b]IGHG-guideline not yet published

the homepage of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and at the LESS group homepage (www.nachsorge-ist-vorsorge.de) in Germany.

22.4 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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