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Treatment Recommendations for Children and Adolescents with Hodgkin`s Lymphoma in Russia

Based on the Experiences of the DAL/GPOH-HD Trials

suggested by

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1 GENERAL INFORMATION

1.1. SYNOPSIS

Indication	Hodgkin's lymphoma in childhood and adolescence – first line treatment
Therapy	All first line patients get two cycles of OE*PA. Patients in TG-1 do not receive further chemotherapy. Patients in TG-2 and -3 receive either COPDAC for two or four cycles respectively. After chemotherapy all patients receive reduced involved field (RIF) radiotherapy with a total dose of 20 Gy to the initially involved lymph node areas.

1.2. RATIONALE FOR THE TREATMENT RECOMMANDATIONS

1.2.1. PRIOR EXPERIENCE OF THE DAL / GPOH-HD STUDY GROUP

These recommendations are built on the experience from the successive DAL / GPOH therapy studies which step by step optimised the treatment of paediatric Hodgkin's lymphoma starting in 1978 and established the de facto treatment standard in the participating countries [1-15].

1.2.1.1. First Study: DAL-HD 78

Already the first study DAL-HD 78 set the general therapeutic paradigm: Chemotherapy starting with 2 courses of intense and effective OPPA (followed by COPP consolidation in intermediate and advanced stages) plus radiotherapy. In study HD 78 radiotherapy consisted of 36 – 40 Gy to the involved field and of either 36-40 or 18 – 20 Gy at a randomised basis to the adjacent fields [1]. Later studies modified treatment within this framework mainly with the objective to reduce acute and long-term toxicity while preserving good treatment results.

1.2.1.2. Second Study: DAL-HD 82

In the second study DAL-HD 82 [1,2], patients for the first time were divided into three treatment groups (TG-1, TG-2, TG-3) based on stage:

TG-1: stages I / IIA

TG-2: stages IIB / IIIA, later included stages I_E / II_EA

TG-3: stages IIIB / IV, later included stages II_EB / III_E.

The number of consolidation COPP cycles was scaled according to treatment group (0, 2, 4, respectively). Irradiation volume was reduced from extended to involved field. Indication for splenectomy was limited [3] and the number of splenectomies dropped to about 40%. Radiation doses were reduced to 35 – 30 – 25 Gy in TG-1, TG-2, TG-3, respectively. In case of insufficient response to chemotherapy the radiation dose was increased by 5 – 10 Gy. 5-year-EFS rates of 99%, 96%, and 90% in TG-1, TG-2, and TG-3, respectively [2] were observed. Due to the excellent long-term results [4,5] the therapy plan of DAL-HD 82 for a long time was regarded the gold standard.

1.2.1.3. Third Study: DAL-HD 85

After the gonadotoxic effect of procarbazine has become apparent [6], this drug was completely eliminated from OPPA–COPP chemotherapy in study DAL-HD 85. Chemotherapy was OPA-COMP, so that in the first two cycles only three agents were administered and procarbazine was replaced by methotrexate in consolidation. Involved field radiotherapy was dosed according to TG with 35 - 30 - 25 Gy, respectively [2]. By eliminating procarbazine fertility in boys indeed was preserved [6,7], but treatment efficacy was compromised: The 6-year EFS rates in the three treatment groups dropped to 85% (TG-1), 55% (TG-2), and 49% (TG-3) [1,2]. However, nearly all patients could be salvaged by relapse therapy, and an overall survival rate of 98% after 10 years in the total study group was seen [4,5].

1.2.1.4. Fourth Study: DAL-HD 87

Therefore in the fourth study DAL-HD 87 procarbazine was reintroduced in all 6 cycles of TG-3 and in the COPP cycles of TG-2 while it was still not administered in the OPA cycles of TG-1 and TG-2. In addition, the radiation dose was further reduced to 30 – 25 - 20 Gy for TG-1, TG-2, and TG-3, respectively [2]. Indication for splenectomy was further restricted so that the spleen only in 29% of the patients was removed. The results of this study re-produced the rates for

EFS of TG-1 in DAL-HD 85 and of TG-3 in HD 82, whereas EFS in TG-2 was worse than in HD 82. In addition, the problem of gonadotoxicity in male patients was still unsolved due to the procarbazine in COPP [2,4].

1.2.1.5. Fifth Study: DAL-HD 90

Therefore initial therapy in the DAL-HD 90 study was changed and re-intensified. All girls got OPPA again. Boys received OEPA, i.e. OPPA with procarbazine replaced by 500 mg/m^2 etoposide per cycle distributed over 4 days, in the hope that this would preserve fertility [8]. Splenectomy was abandoned and the radiotherapy dose was further reduced to 25 – 25 - 20 Gy for TG-1-3, respectively. Reduced involved field (RIF) irradiation has been introduced which includes only the initially involved nodes and an appropriate safety margin taking into account the involved lymph node area [9]. A further innovation was the up-front centralised review of images and data resulting in individualised radiotherapy proposals in accordance with the protocol guidelines [10]. This central review procedure has been used also in the following studies and contributed decisively to an improved quality management of the patient allocation to treatment groups and of radiotherapy. Also the response evaluation and its consequences for radiotherapy have been increasingly included in the centralised review procedure.

With this strategy, a 5-year EFS rate of 91% was achieved with OPPA and 89% with OEPA. Overall survival after 5 years was 98% in both groups [8]. The results are comparable to the very good results of the DAL-HD 82 study. By introducing etoposide the infertility rate of boys was significantly reduced in TG-1, while about half of the male patients in TG-2 and TG-3 still showed abnormal FSH values due to the COPP cycles [11].

1.2.1.6. Sixth Study: GPOH-HD 95

A major concern apart from infertility in boys has been the development of treatment related secondary malignancies. The rate of secondary haematological malignancies (leukaemias and NHL), which occur mostly 1 – 10 years after therapy, is very low. The estimated risk after 22 years is about 1% for the patients in the studies DAL-HD 78 to DAL-HD 87 [12]. After the introduction of etoposide in DAL-HD 90, no increase of the incidence of secondary leukaemias has been observed so far [13].

On the other hand, the number of non-haematological secondary tumours still increases after a latency period of 20 and more years [13]. The cumulative risk of secondary solid tumours (SST) for the DAL-HD study patients is 10.0% (SE 2.0%) after 22 years. The most important risk factor

for the development of secondary solid tumours (SST) is radiotherapy. 29 of the overall 36 SST (81%) observed within the 5 first DAL-HD studies have occurred in or at the border of the radiation fields.

Therefore in the GPOH-HD 95 study the dose of radiotherapy was reduced to 20 Gy in all treatment groups and reduced involved field radiotherapy was systematically considered for all patients. In addition, radiotherapy was omitted in patients with complete remission (CR) at the end of chemotherapy [14,15] in order to reduce the number of patients at risk for radiotherapy associated secondary solid tumours and for other radiation induced late effects like thyroid disorders and cardiac diseases.

Event free survival after 5 years was 88% for all patients; overall survival 97%. In TG-1 there was no significant EFS difference between patients with (94%) and without (97%) radiotherapy. Therefore omission of radiotherapy has been adopted as standard treatment for patients in TG-1 who achieved CR after two cyles of chemotherapy.

However, in TG-2 and TG-3 omission of radiotherapy for CR patients led to a significant decrease in EFS: 79% without versus 91% with radiotherapy. Therefore radiotherapy for all patients in TG-2 and TG-3 was re-introduced as standard in the following study [14, 15].

1.2.1.7. Seventh Study: GPOH-HD 2002 Pilot study

In GPOH-HD 2002 Pilot, all boys received an intensified OE*PA therapy (20% more Etoposide) and COPDAC instead of the COPP cycles.

*1.2.1.7.1. Rationale for intensified OE*PA and toxicity results*

In the previous studies DAL-HD 90 and GPOH-HD 95, boys showed a tendency for lower EFS than girls. This may or may not be related to girls receiving OPPA and boys receiving the less gonadotoxic OEPA. Male gender has been reported as unfavourable prognostic factor in the adult setting and is included in the international prognostic score [16].

Based on the interpretation that OEPA might be less effective than OPPA, OEPA was intensified in the GPOH-HD 2002 Pilot study extending etoposide administration from 4 to 5 days (OE*PA).

The total etoposide dose increased from 4 to 5 x 125 mg/m²/d as 2-hour infusion per OE*PA cycle. This corresponds to a cumulative dose of 1250 mg/m² in 2 OE*PA cycles which is still far below the critical cumulative dose of 2000 mg/m² above which an increased risk of secondary AML was described [17-19] Internationally, the increased cumulative etoposide dose is still below that of other studies, e.g. the VBVP cycles of the French study MHD 90 (single dose 167

mg/m^2, cum. dose 2000 mg/m²) or the VEEP cycles of the Australian – New Zealand study (single dose 150mg, cum. dose 3000 mg/m²).

Feasibility of intensified OE*PA was confirmed based on 510 OE*PA blocks for 255 patients from a total of 308 registered male patients (status: 01.08.2005). Apart from the expected haematoxicity (Table 1) CTC degree 3 or 4 toxicity were rare.

Table 1 Toxicity evaluation for OE*PA in the GPOH-HD 2002 Pilot Study

According to CTC criteria of the NCI; for 510 OE*PA blocks documented so far

Toxicity	Number of documented incidences					
	Not documented	0	I°	II°	III°	IV°
Performance status	47	179	200	73	11	2
Haemoglobine	9	119	164	179	34	5
Leukocytes	1	27	63	136	208	75
Neutrophils	120	35	28	35	105	187
Platelets	1	447	25	29	5	3
Infection	52	355	35	55	12	1
Fever	7	377	64	55	7	0
Nausea	184	197	95	31	2	1
Vomiting	7	359	85	59	0	0
Stomatitis	3	339	74	64	22	8
Constipation	11	368	37	77	17	0
Diarrhoea	10	428	50	16	6	0
Allergy	192	312	3	3	0	0
Pain	179	249	48	27	6	1
Neurotoxicity sensory	13	434	52	7	2	2
Neurotoxicity motor	13	449	32	10	6	0
Neurotoxicity central	194	310	4	0	0	2
Cardiotoxicity	291	214	2	2	0	0
Creatinine	17	465	23	5	0	0
Proteinuria	256	246	8	0	0	0
Haematuria	251	251	8	0	0	0
Creatinine clearance	365	140	3	1	0	0

1.2.1.7.2 Rationale for COPDAC and toxicity results

The experiences of previous studies show that procarbazine is mainly responsible for the infertility of treated boys. The percentages of elevated FSH levels in postpubertal male patients depended on the cumulative dose of procarbazine: 28.9% after two OPPA, 43.8% after two OPPA and two COPP, and 62.5% after two OPPA and 4 COPP cycles [6].

On the other hand no increased FSH levels were observed in those boys who had been treated in the DAL-HD 85 study [11] or who had only received OEPA in TG-1 of the DAL-HD 90 study [9].

Therefore in GPOH-HD 2002 Pilot procarbazine was replaced by dacarbazine which is less likely to cause infertility in males and a premature menopause in females. Our previous studies DAL-HD 82 and DAL-HD 87 showed that procarbazine cannot be dropped without being replaced by an appropriate substitute.

A literature research showed that dacarbazine (DTIC) could be an appropriate substitute for procarbazine [20, 21]. Dacarbazine acts like procarbazine as an alkylating agent and inhibits both the DNA and the RNA synthesis. It is an approved drug which has been extensively used in Hodgkin's lymphoma. Even after 6 ABVD cycles male patients are unlikely to become permanent azoospermia.

In contrast to procarbazine, DTIC is administered intravenously. This reduces another possible problem – drug non-compliance.

In 1972 dacarbazine was tested by Frei [2o] as a monotherapy in pre-treated patients. He achieved „objective remissions" in 56% at a daily dosage of 250 mg/m² for 5 days at intervals of 3 weeks. Klener and Donner [21] treated 10 HD patients, who had become resistant to combination chemotherapy, with DTIC, 300 mg/m^2 i.v. for 5 days running at an interval of 4 weeks which led to CR in 2 patients and PR in 7 patients. They particularly emphasized that DTIC causes only a minor myelosuppression. Both publications put together, „objective remission" was achieved in 67% and complete remission in 13%. Since a response rate of 69% (38% CR) was achieved with a dose of 3000 mg procarbazine, administered in 3-week intervals in 366 patients (Carter et al., 1973) an approximate equivalence factor of about 2.4 may be assumed. Thus a dose of 750 mg/m² dacarbazine used in the proven ABVD cycles would correspond in effectiveness to approximately 1800 mg/m^2 procarbazine. It should therefore be equivalent to the procarbazine dose of 1400 mg/m^2 applied in the COPP cycle. In this protocol DTIC is to be administered over three days at the beginning of the COPDAC cycle in a dose of 250 mg/m^2 in 30-minute infusions to achieve the highest possible dose intensity.

The evaluation of chemotherapy toxicity for 473 COPDAC blocks of 170 male patients (status: 01.06.2005). The toxicity profile is detailed in Table 2.

Table 2 Toxicity evaluation for COPDAC in the GPOH-HD 2002 Pilot Study

According to CTC criteria of the NCI of 473 COPDAC blocks documented so far

Toxicity	Number of documented incidences					
	Not documented	0	I°	II°	III°	IV°
performance status	59	230	159	23	1	1
Haemoglobin	6	208	177	67	15	0
Leukocytes	5	207	151	83	25	2
Neutrophils	104	183	80	62	31	13
Platelets	5	448	14	3	2	1
Infection	38	393	24	14	4	0
Fever	10	407	32	22	2	0
Nausea	140	281	51	1	0	0
Vomiting	4	438	21	10	0	0
Stomatitis	2	434	35	2	0	0
Constipation	12	411	15	33	2	0
Diarrhoea	11	452	8	2	0	0
Allergy	164	300	7	1	1	0
Pain	156	269	24	13	11	0
Neurotox. sensorial	10	378	71	10	4	0
Neurotox. motorical	12	408	46	6	1	0
Neurotox. central	170	300	0	0	0	3
Cardiotoxicity	353	118	2	0	0	0
Creatinine	20	423	27	3	0	0
Proteinuria	259	208	6	0	0	0
Haematuria	252	217	4	0	0	0
Creatinine clearance	346	121	6	0	0	0

These preliminary data indicate that the COPDAC block and with it the DTIC are well tolerated.

One SUSAR (suspected unexpected serious adverse reaction) was reported most probably related to DTIC. The patient developed a delayed type hypersensitivity reaction after the second COPDAC cycle. Consequently he presented with acute renal failure, shock and rhabdomyolysis. In the literature [22] only few cases of irreversible acute renal failure have been described after treatment with DTIC. However, as to our knowledge this is the first case of severe rhabdomyolysis possibly related to DTIC. The patient died of progressive multi-organ failure.

An interim analysis on efficacy in the GPOH-HD 2002 pilot study was performed as of 2006-10-31. At a median observation time of 24 months PFS curves of girls (N=199) receiving OPPA-COPP and boys (N=205) receiving OEPA-COPDAC in TG-2+TG-3 are super-imposable with PFS rates 90% (sSE=2%) at 24 months. This is in line with the experience of previous studies. Based on 2 year PFS-rates OPPA-COPP and OEPA-COPDAC appear to be exchangeable treatment options for TG-2+3. No etoposide induced secondary leukaemias were observed.

Although at the moment the efficacy of COPDAC is evaluated in the EuroNet-PHL C1 trial as a randomization between COPP and COPDAC, within this recommendation for Russia COPDAC and not COPP is choosen mainly because of the unavailability of procarbazine in Russia. However, the use of COPDAC seems reasonably safe and effective enough to recommend it to a group of patients for whom access to procarbacine is difficult. Based on these results it is recommended that all patients will receive an intensified OE*PA and depending on treatment group between 0 and 4 COPDAC cycles (TG1 – TG3). Due to the fact that response evaluation is rather complicated and is performed in the EuroNet-PHL group mainly via central review, all patients treated according to this recommendation should receive 25 Gy to all initially involved lymph node regions independent of the response to treatment.

2. DIAGNOSTICS

If Hodgkin's lymphoma is suspected, an open biopsy should be obtained as soon as possible (exception large mediastinal tumour see chapter 4).

2.1. CONFIRMATION OF DIAGNOSIS

The histopathological diagnosis is based on a biopsy of a lymph node or as the case may be of a biopsy of another primarily involved organ. Biopsies using a fine needle are not appropriate.

Reference pathology should be done to confirm the diagnosis.

2.2. CLINICAL AND LABORATORY DIAGNOSTICS BEFORE / DURING THERAPY

2.2.1. Diagnostics prior to chemotherapy

Exact clinical history including:

- previous and concomitant diseases (e.g. **paraneoplastic phenomena** such as nephrotic syndromes and other autoimmune diseases),
- systemic symptoms and
- prior treatment.

Clinical examination

- detailed documentation of all **palpable lymph nodes and their localisation**.
- examination and inspection of Waldeyer's ring preferably by ENT-physician.
- Palpation of spleen and liver

Laboratory examinations:

- Complete blood count, erythrocyte sedimentation rate, ALAT (GPT), ASAT (GOT), GGT, LDH, AP, creatinine and albumin in the serum, fibrinogen, Immunoglobuline A, G, M
- Protein electrophoresis: gamma-globuline and alpha-2-globuline
- Baseline virology recommended to include serologic examinations for antibodies against VZV, EBV, CMV, HSV, HIV, toxoplasmosis, hepatitis A, B, C (HCV-PCR).

Functional examinations

- ECG

- Echocardiography
- EEG (optional)

For boys cryopreservation of semen should be offered to young male patients if sexually mature

2.2.2. Diagnostics assessment before each course of chemotherapy

Before start of each chemotherapy cycle:

- Presence of infections
- detailed clinical examination
- Lansky/Karnofsky's score depending on age
- blood counts including differential blood count
- ALAT, ASAT, GGT, bilirubin, creatinine

Further diagnostic measures (such as ECG, lung function etc.) are carried out according to the individual circumstances of the patient.

2.3. IMAGING DIAGNOSTICS

2.3.1. Initial staging

Cross sectional imaging is mandatory. It should preferably be performed according to options A or B, see below.
Low dose chest CT should be performed with weight-dependent dosage if possible.

A) CT chest with mediastinum, MRI neck / abdomen / pelvis

CT examination:

CT examination of thorax is mandatory, since lung foci can be best diagnosed with CT. (Recommendations for CT examination performance see B).

MRI examinations should include the following sequences:

- **neck**: transversal and coronal T2 fat saturated T2 (T2-TIRM, T2-STIR)
- **thorax**: If performed in addition to chest CT an MRI examination of lung and mediastinum should provide ECG triggered transversal sequences to avoid pulsation artefacts.

- **abdomen**: transversal T2 fat saturated and T1-FLASH 2d dynamic in arterial, portal venous and venous phase
- **pelvis**: T1-SE transversal, T2- fat saturated transversal and coronal, T1-SE-transversal after contrast agent with fat saturation

B) CT neck / thorax / abdomen / pelvis

Recommendation for examination performance:

examination region:	epipharynx to lower edge of symphysis
layer thickness:	reconstructed 5 mm layers
oral contrasting:	yes
i.v. contrasting:	depending on KG 1.5 – 2.0 ml/kg KG (recommended up to 10 kg KG 2 ml/kg, up to 40 kg KG 1.5 ml/kg, from 40 kg 60 ml; choose delay according to device so that a parenchymal phase of liver and spleen is achieved)
reconstruction:	lung: sharp kernel and pulmonary window, mediastinum with involvement of axillae, supra- and infraclavicular region: soft kernel and mediastinal window, abdomen and pelvis involving inguinal region: abdominal window (e.g. W 400/C 60)

Additional imaging procedures

Sonography of spleen and liver are mandatory and of lymph nodes are recommendable.
Bone scan: This examination is only performed in patients with suspected skeletal involvement.

2.4. ASSESSMENT OF INVOLVED REGIONS

2.4.1. Assessment of nodal involvement

2.4.1.1. Assessment of lymph node involvement

1. If the largest diameter of a lymph node or a lymph node conglomerate is smaller than 1 cm the region is considered not involved. Unidentified micro-findings do not impair therapy results according to previous experience.

2. If the largest diameter of a lymph node or a lymph node conglomerate exceeds 2.0 cm the region is considered involved.

3. If a lymph node or a lymph node conglomerate has a diameter of 1.0 – 2.0 cm the region is considered questionably involved and the decision on involvement of this region is made including further criteria, such as clinical data, ultrasound findings, proximity to larger involved region or response to treatment (e.g. if in a questionably involved region almost no response is seen after chemotherapy, while other definitively involved regions responded well, then this region is considered not initially involved).

2.4.1.2. Assessment of Waldeyer's ring

1. Involvement is defined by clinical assessment preferably by ENT physician and is sometimes not measurable: involvement yes/ no; localisation left/right;
2. Biopsy is not required and not appreciated since too invasive

2.4.2. Assessment of extra-nodal involvement

2.4.2.1. Pleura and pericardium

Involvement of the pleura is assumed if

- the lymphoma is contiguous with the pleura without fat lamella or
- the lymphoma invades the chest wall or
- a pleural effusion occurs which can not be explained by a venous congestion.

Pericardial involvement is assumed if

- the lymphoma has a broad area of close contact towards the heart surface beyond the valve level (ventriculus area) or
- a pericardial effusion occurs.

Pleura and/or pericardial involvement are generally considered E-lesions.

2.4.2.2. Extra-nodal involvement

Extra-lymphatic structures or organs that are infiltrated per continuum out of a lymphatic mass are termed E-lesion (examples: lung, intestine, bones) and do not automatically qualify for stage IV. **Exceptions: Liver or bone marrow involvement always implies stage IV.**

2.4.3. Organ involvement

2.4.3.1. Lung involvement

A disseminated lung involvement (implying stage IV) is assumed if

- there are more than three foci or
- an intrapulmonary focus has a diameter of more than 10 mm.

If a smaller than 10 mm involvement is seen, stage IV is not assumed since these patients have a very good prognosis without upstaging.

E-lesion of the lung is restricted to one pulmonary lobe or perihilar extension with homolateral hilar lymphadenopathy.

2.4.3.2. Liver and spleen involvement

- Liver involvement implies always stage IV.
- Exclusive splenic involvement without other lymphatic disease is classified as stage I.
- Mere enlargement of liver / spleen only is not considered as involvement.
- Focal changes in the liver / spleen structure that are **tumour suspicious** in ultrasonography are considered involved. In case of doubtful involvement of liver or spleen (e.g. structures atypical of tumour in sonography or MRI) the liver / spleen is considered involved if these lesions disappear or at least are significantly reduced in size after two cycles of chemotherapy.

2.4.3.3. Bone / bone marrow involvement

Bone involvement is assumed if

- A bone biopsy is positive **or**
- CT bony window is positive **or**
- A positive bone scan is confirmed by either CT or MRI.
- MRI positive in bone and adjacent soft tissue (T2 fat saturated sequences).

Bone marrow involvement is assumed if bone marrow biopsy is positive

A bone marrow biopsy is mandatory unless stage I or IIA. Bone or bone marrow involvement implies stage IV.

2.5. INDICATIONS FOR INVASIVE DIAGNOSTIC MEASURES

2.5.1. Bone marrow biopsy

All patients with a stage >IIA get a bone marrow biopsy in one or two regions.

2.5.2. Selective laparoscopy

Selective laparoscopy **without splenectomy** is indicated only in rare cases where involvement can not be clarified by use of CT/MRI or sonography and the above mentioned regulations.

2.5.3. Ovariopexy

Whenever an iliac lymph node region is to be irradiated in girls lateral movement of the adjacent ovary should be considered.

Ovariopexy is particularly recommended if both ovaries are expected to receive a dose of more than 5 Gy which may lead to significant long-term ovarian impairment. Using opposed fields with 25 Gy, this can be usually be avoided, if the ovary is more than 2 cm from the adjacent field (shield) border.

When performing an ovariopexy sutures should be marked with clips! After consultation with the radiotherapist surgery should be carried out immediately before infra-diaphragmatic irradiation.

2.6. RESTAGING

2.6.1. First restaging after 2 cycles of chemotherapy

All initially involved regions are checked by CT/MRI/ultrasound examinations. However, patients with suspected progression get a complete staging of all lymph node regions.

2.6.2. Second restaging after full chemotherapy in therapy groups 2 + 3

After 4 or 6 cycles of chemotherapy all initially involved regions of the patients in TG-2 +3 are re-examined. CT / MRI / ultrasound at best between day 10 and 14 after the last application of chemotherapy in the fourth or sixth cycle respectively..

2.6.3. Follow-up

Follow-up starts six weeks after completion of therapy according to the recommendations (Tab. 3)

Table 3 Recommendations for follow-up examinations

	Time					
Procedures	**In 1st year First follow-up 6 weeks after end of treatment**	**In 2nd year**	**In 3rd year**	**In 4th year**	**In 5th year**	**from 6th year on**
Clinical history and examination	4 - 8x	4 - 8x	4x	2x	2x	Individually
Blood counts, ESR	4x	4x	2x	2x	2x	
Sonography abdomen and lymph nodes	4x	4x	2x	2x	2x	
MRI in involved region	2x	1-2x	1x	1x	1x	
CT thorax in case of lung involvement	2x	1x	Individually			
After radiation of mediastinum and/or lung: Functional lung evaluation	1x	Individually				
After neck radiation: thyroidsonography, fT4, TSH	1x	1x	1x	1x	1x	
ECG / echo-CG		1x			1x	
After RT > 25 Gy of infraclavicular region, axillae, mediastinum or lungs: breast cancer screening	To be considered in women above age 25 annually					

3. STAGE CLASSIFICATION AND DEFINITION OF THERAPY OUTCOME

3.1. STAGE CLASSIFICATION

Stage classification is performed according to Cotswolds revision of the classical Ann Arbor staging system. Table 4 details the definition of lymph node regions and extra-nodal sites on which staging is based.

Table 4 Independent lymph node regions

Independent lymph node regions are:

- **Waldeyer's ring (left and right)**
- **cervical (left and right) and supraclavicular (left and right) with sub-regions relevant for irradiation:**
  - upper neck: up to upper edge of larynx
  - lower neck: up to supraclavicular fossa
- **infraclavicular (left and right)**: subpectoral on the thoracic wall
- **axillar (left and right)**
- **lung hilus (left and right)**: bronchopulmonary LN
- **mediastinum with sub-regions relevant for irradiation**:
  - upper mediastinum: down to bifurcation
  - middle mediastinum: hilus down to subcarinal region
  - lower mediastinum: down to diaphragm
- **supradiaphragmatic:** diaphragmatic recessus
- **spleen**
- **splenic hilus**
- **liver hilus**
- **mesenteric**: mesentery, mesocolon
- **paraortic:** coeliac, paraaortocaval, pararenal, paralienal, parapancreatic
- **iliac (left and right)**: parailiac
- **inguinal (left and right)**: inguinal, femoral

Table 5 Stage classification Hodgkin's lymphoma

Stages of Hodgkin's lymphoma according to the Cotswolds revision of the Ann Arbor staging system

I Involvement of a single independent lymph node region or lymph node structure

II Involvement of 2 or more lymph node regions on the same side of the diaphragm

III Involvement of lymph node regions or lymph node structures on both sides of the diaphragm

IV Involvement of extra-nodal sites beyond "E"-sites

Table 6 Annotations to stage definitions

A. No B symptoms B. At least one of the following systemic symptoms a. Inexplicable weight loss of more than 10% within the last 6 months b. Unexplained persisting or recurrent temperature above 38 °C c. Drenching night sweats E. Involvement of a single extra-nodal site contiguous or proximal to known nodal site. (For the distinction between stage IV and the E-stages see chapter 2.4.2.)

3.2. DEFINITION OF TREATMENT RESPONSE

3.2.1. Local response definitions for nodal involvement with measurable tumour volume

At staging all measurable nodal sites excepted spleen and Waldeyer's ring are grouped in **separately measurable reference volumes**. Reference volumes can include multiple sites if these are contiguous.

The composition of these reference volumes is defined and documented. Initial volumes of reference volumes are measured.

Volumes are approximated as ellipsoids. If a, b, c denote the principal axes of the ellipsoid the volume is calculated as $V= (a \times b \times c)/2$.

The overall response to treatment is determined according to a systematc assessment of tumour response in all involved sites.

In those sites where the tumour is measurable from CT/MRI scanning the change in tumour volume is compared to the original pre-treatment reference volume and then assigned a treatment response for that local site.

3.2.1.1. Local Complete remission (localCR)

A reference volume is in "local complete remission"(in short: localCR) if:

- the residual tumour volume is less or equal 5% of the reference volume (CT/MRI) **and**

- the residual tumour volume is less or equal 2 ml.

3.2.1.2. Local complete remission unconfirmed (localCRu)

A reference volume is in "local complete remission unconfirmed "(in short: localCRu) if:

- No localCR **and**
  - the residual tumour volume is less or equal 25% of the reference volume (CT/MRI) **or (!)**
  - the residual tumour volume is less or equal to 2 ml

3.2.1.3. Local partial remission (localPR)

A reference volume is in "local partial remission"(in short: localPR) if:

- No localCR or localCRu **and**
- the residual tumour volume is less or equal 50% of the reference volume (CT/MRI) **or** the residual tumour volume is less or equal 5 ml (to saveguard against artefacts due to measurement errors).

3.2.1.4. Local no change (localNC)

A reference volume is in "local no change" (in short: localNC) if

- no localCR or localCRu or localPR **and**
- no local Progression

3.2.1.5. Local Progression (localPRO)

A reference volume is in "local progression" (in short: localPRO) if

- The residual tumour volume is larger than 125% of the reference volume or significantly increases compared to the best previous response – be aware of possible measurement error in small tumour volume.

3.2.2. Local response definitions for extra-nodal involvement or for nodal involvement with non-measurable tumour volume

For all extra-nodal sites or for nodal involvement with non-measurable tumour volume three response categories are distinguished by radiological or clinical criteria:

- **Locally undetectable**

- **Locally detectable**
- **Locally progressive**

Only “Locally undetectable” is consistent with overall CR.

Note: In case of multi-focal bone or bone marrow involvement multiple sites are assessed separately. .

3.2.3. Overall (patient level) response definitions

Overall (patient level) response categories are obtained from the worst local response in reference volumes and the worst local response in non measurable nodal or extra-nodal disease as illustrated in the following figure:

Fig. 1. Definition of overall response

		worst local response in nodal reference volumes					
		no involvement	local CR	local CRu	local PR	local NC	local PRO
worst local response in extranodal or non-measurable nodal regions	no involvement		overall CR	overall CRu	overall PR	overall NC	overall PRO
	undetectable	overall CR	overall CR	overall CRu	overall PR	overall NC	overall PRO
	still detectable	overall CRu	overall CRu	overall CRu	overall PR	overall NC	overall PRO
	local PRO	overall PRO	overall PRO	overall PRO	overall PRO	overall PRO	overall PRO

legend: overall CR, overall CRu, overall PR, overall NC, overall PRO

3.2.3.1. Complete remission (CR)

"Complete remission“(in short: CR) is achieved if in restaging

- all disease symptoms have disappeared **and**
- no new lymphatic or extra-lymphatic lesions have occurred **and**
- ***all*** initially involved extra-nodal sites or involved regions with non-measurable tumour volume are locally undetectable **and**
- ***all*** reference volumes are in localCR

3.2.3.2. Complete remission unconfirmed (CRu)

"CR unconfirmed“(in short: CRu) is achieved if in restaging

- no CR **and**
- all disease symptoms have disappeared **and**
- no new lymphatic or extra-lymphatic lesions have occurred **and**
- ***all*** initially involved extra-nodal sites or involved regions with non-measurable tumour volume are not locally progressive **and**
- ***all*** reference volumes are at least in localCRu

3.2.3.3. Partial remission (PR)

"Partial remission” (in short: PR) is achieved if in restaging

- no CR or CRu **and**
- all disease symptoms have disappeared **and**
- no new lymphatic or extra-lymphatic lesions have occurred **and**
- ***all*** initially involved extra-nodal sites or involved regions with non-measurable tumour volume are not locally progressive **and**
- ***all*** reference volumes are at least in localPR

3.2.3.4. No change (NC)

"No change” (in short: NC) is achieved if in restaging

- no CR or CRu or PR **and**
- no PRO

3.2.3.5. Progression (PRO) / Relapse (R)

Progression / Relapse of the disease occurs if

- recurrence or occurrence of new disease symptoms which can not be explained otherwise **or**
- occurrence of new lymphatic or extra-lymphatic lesions **or**
- ***at least one*** initially involved extra-nodal site or involved region with non-measurable tumour volume is locally progressive **or**
- at least one reference volume is in localPRO

Biopsy of an enlarging region or new lesion is mandatory.

A progression / relapse of the disease is called

- **progression** if it occurs until three months after the end of therapy (in general last day of radiotherapy application.
- **early relapse** if it occurs between three and twelve months after the end of therapy.
- **late relapse** if it occurs later than twelve months after the end of therapy.

4. THERAPY PLAN FOR PRIMARY THERAPY

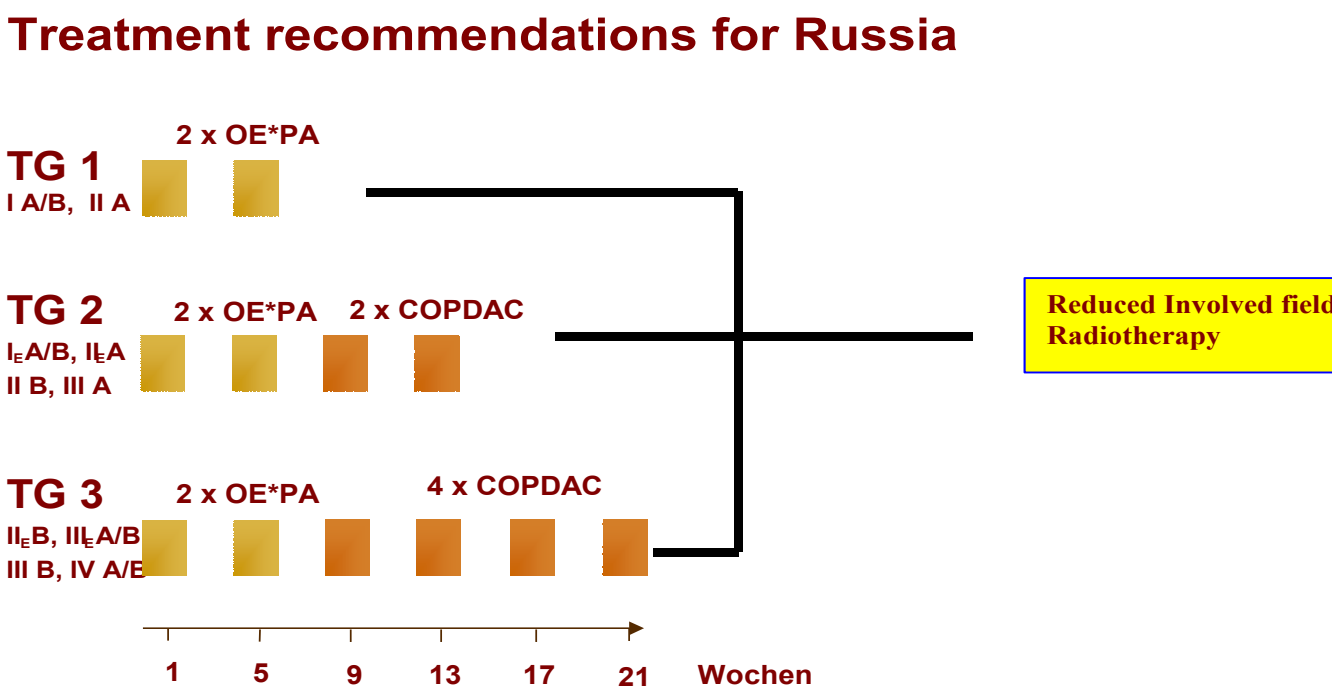

Fig. 2 Overview treatment plan

4.1. TREATMENT GROUPS

Patients are divided into treatment groups (TG) according to the stage

Treatment groups are as follows:

TG-1: patients of stages I A/B and II A

TG-2: patients of stages I_EA/B, II_EA, II B or III A

TG-3: patients of stages II_EB, III_EA/B, III B or IV A/B

4.2. TREATMENT GROUP 1 (TG-1)

All patients receive two cycles of OE*PA followed by involved field radiotherapy of all initially involved regions with 20 Gy. Radiation therapy should start by day 14 - 28 after the last dose of chemotherapy in the second OE*PA-cycle **at latest**.

4.3. TREATMENT GROUP 2 AND 3 (TG-2, TG-3)

After initial staging and assignment to treatment groups 2 or 3, patients receive two cycles of OE*PA, followed by two (TG-2) or four (TG-3) cycles of COPDAC. After chemotherapy all

patients receive involved field RT of all initially involved lymph node regions with 20 Gy independent of the response to chemotherapy.

Radiotherapy begins 14 - 28 days after last dose of prednisone/prednisolone of the 4th respectively 6th chemotherapy cycle if the following requirements are fullfilled

- general condition satisfactory
- WBC over 2,000 / mm^3
- ANC over 500 / mm^3
- platelets over 80,000 / mm^3

4.4. CHEMOTHERAPY PLANS

The first cycle of OE*PA starts immediately after completion of staging. In the rare case of a staging laparoscopy, the first cycle of OE*PA should start about 5 days after surgery. Details of chemotherapy administration are available in the chemotherapy drug monographs in the appendix.

The subsequent chemotherapy cycle starts on d29 of each cycle when the following criteria are fulfilled:

- general condition satisfactory
- WBC over 2,000 / mm^3
- ANC over 500 / mm^3
- platelets over 80,000 / mm^3
- no contraindication to any of the prescribed drugs

In case of patients with an expected delay of more than one week, please contact your national Hodgkin`s lymphoma expert.

Severe side effects are not expected with OE*PA or COPDAC. Chemotherapy should only be interrupted in case of severe inter-current infections. In parallel to chemotherapy patients may receive hyperhydration with 2.5-3 l/m^2 per day of glucose-saline solution.
For oncological emergencies in patients with initially large tumour mass please see chapter 4.10.

4.4.1. OE*PA

Application schedule and dosage of cytotoxic drugs during a cycle are shown in Table 7. After each cycle there is a treatment-free interval between day 16 and 28. The next cycle starts on day 29.

Table 7 OE*PA scheme

Prednisone/prednisolone 60 mg/m^2/day p.o. divided into 3 doses day 1 – 15	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Vincristine 1.5 mg/m^2 i.v., max. SD 2 mg day 1 + 8 + 15	•							•							•
Doxorubicine 40 mg/m^2 as 1-6 hour infusion day 1 + 15	•														•
Etoposide/Etopophos 125 mg/m² as 1-2 hour infusion day 1 – 5	•	•	•	•	•										
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

4.4.2. COPDAC

Application scheme and dosage of cytostatic drugs during a cycle are shown in Table 8. After each cycle there is a treatment-free interval between day 16 and 28. The next cycle starts on day 29.

To minimise toxicity to the urinary tract, there is the option to give the uroprotector mesna along with every application of cyclophosphamide.

Dacarbazine is highly emetogenic. Therefore 5-HT3-antagonists, possibly supplemented with dexamethasone (optional) or neuroleptics (e.g. levomepromazin), are recommended for antiemesis.

Table 8 COPDAC scheme

Prednison/Prednisolone 40 mg/m^2/day p.o. divided into 3 doses day 1 – 15	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Dacarbazine 250 mg/m^2 as 15 - 30-min. inf. day 1 – 3	•	•	•												
Vincristine 1.5 mg/m^2 i.v. max. SD 2 mg day 1 + 8	•							•							
Cyclophosphamide 500 mg/m^2, 60-min. inf. day 1 + 8 Intravenous hydration with glucose/ saline solution at a rate of 3 l / m^2/ 24 hours	•							•							
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

4.5. DOSE MODIFICATIONS

Since chemotherapy is well tolerated no detailed provisions for dose modifications are given, even in patients with haematotoxicity CTC grade 4. A short therapy delay may be indicated in a few cases. For the criteria for the continuation of chemotherapy see section 4.4.

4.6. CONTRACEPTION

All patients are advised that during chemo-/radiotherapy and up to one year afterwards procreation of children is not recommended, there is a risk of an adverse effect on the fetus. The treating physician should advise about methods of contraception individually..

4.7. SIDE EFFECTS OF CHEMOTHERAPY

General acute side effects of chemotherapy include: nausea, vomiting, weight loss and alopecia. General late side effects of chemotherapy include: increased risk of secondary malignancies, infertility or premature menopause, and increased cardiac event risk.

For additional information on side effects please check chemotherapy drug monographs in the appendix.

4.7.1. Etoposide

Acute side effects of etoposide include: allergic reaction, mucositis, peripheral neuropathies CNS toxicities, mild bone marrow depression and secondary leukaemia.

4.7.2. Dacarbazine (DTIC)

Dacarbazine is highly emetogenic. Diarrhea, influenza-like symptoms, allergic skin reactions, fever, photosensitization, local vein irritation as well as flush symptoms can occur during or after injection. Bone marrow toxicity is generally low. Rarely liver, kidney and CNS toxicities (apathy, seizures) occur. A mutagenic, carcinogenic and teratogenic effect for DTIC has been demonstrated in animal experiments. During the GPOH-HD 2002 Pilot study one patient died with rhabdomyolysis after DTIC.

4.7.3. Vincristine (VCR)

Acute side effects after application of vincristine are: peripheral neuropathy, constipation, rarely syndrome of inappropriate ADH secretion (= SIAD). In case of severe peripheral neuropathy, especially in motor disturbances or paralysis of hands and/or legs a replacement of Vincristine by Vinblastine in a dose of 6 mg/m^2 is recommended.

4.7.4. Cyclophosphamide

Under cyclophosphamide the following side effects can occur: bone marrow depression, increased infection risk, haemorrhagic cystitis.

4.7.5. Adriamycin (Doxorubicine)

Even at a low cumulative dose adriamycin can lead to a permanent damage of the heart muscle. The extent of the long-term cardiac risk is unknown. Therefore before starting chemotherapy the heart function has to be examined (echocardiography) and documented. In case of initial damage of the heart function a therapeutic alternative should be discussed with the study chairpersons.

4.7.6. Prednisone/Prednisolone

Changes in the bone metabolism have been detected (especially in patients with leukaemia) which can lead to osteonecrosis. In rare cases an artificial joint replacement may be required. In

addition, the prednisone/prednisolone therapy can lead to reversible retention of water, increase in weight, increased infection risk and psychosis/mental disorders.

4.8. RADIOTHERAPY

All patients should receive radiotherapy using the technique of reduced involved field (RIF) irradiation to all initially involved regions. The target volume includes all initially involved lymph nodes as recorded before chemotherapy with a minimum safety margin of 1 - 2 cm in cranio-caudal direction and lateral directions taking into account the “area” of involvement. Exceptions are the mediastinum, the para-aortic region, and pelvic areas: chemotherapy response is taken into account for the lateral borders to minimise irradiation of sensitive normal tissue. For example in case of mediastinal lymph node involvement the planning target volume (PTV) includes the pre chemotherapy tumour extent with a margin of 1-2 cm in craniocaudal direction. In lateral direction the treated width should cover appropriately the standard mediastinal width including the relevant mediastinal and/or hilar lymph node areas. In case of paraaortal lymph node infiltration the PTV includes the pre chemotherapy tumour extent with a margin of 1-2 cm and the lateral borders take into consideration the post chemotherapy tumour extension plus a security margin of 1-2 cm. The radiation dose is 19,8 Gy. Asymmetric irradiation of the spine should be avoided to prevent growth disorder. Patients with bulky residual disease of more than 100 ml after the end of chemotherapy should be treated with a 10 Gy boost. The boost planning target volume is defined by the tumour extent, after end of chemotherapy with a 1-2 cm safety margin. The boost volume can not exceed the size of the reduced involved field. Adjacent residual masses requiring a boost are taken simultaneously in one field.

4.8.1. Timing of Radiation planning

Radiotherapy should be started as soon as possible after the last day of chemotherapy, i.e. usually 14 – 28 days after the last dose of prednisone.

4.8.2. Side Effects of radiotherapy

Acute side effects:

Acute side effects as moderate mucositis, skin reactions, hairloss, dry mouth, leucocytopenia, and thrombocyctopenia during radiotherapy with low doses are rare and mostly temporary.
Time and intensity of side effects may additionally depend on prior chemotherapy.

Long term side effects:

Radiosensitivity of normal tissues varies with age. Radiation effects are more pronounced in young age (0-6 years) and pre-pubertal children compared to older children or adults. In

general, the radiosensitivity of normal tissues, especially late reacting tissues, decreases with advancing age. Especially high radiosensitivity occurs during periods of growth. Side effects can be aggravated by certain drugs e.g. Adriamycin.

Radiation induced changes in organs and tissues (e.g. hypothyroidism, premature menopause) may develop after long latency periods and may not become clinically evident until puberty or adulthood.
Secondary malignancies (e.g. increased risk of breast cancer) may occur after 15 to 20 years and later.

4.9. SUPPORTIVE CARE

4.9.1. Antibacterial prophylaxis

All patients receive trimethoprim / Sulfamethoxazol (240 mg twice daily for those with surface area 0.5-0.75 m^2; 0.76-1.0 $m^{2;:}$ 360 mg twice daily; over 1 $m^{2\ :}$ 480 mg/ m^2 twice daily all given on monday and tuesday of each week) orally during chemo- and radiotherapy and up to three months after end of chemo-radiotherapy.
If WBC is below 1000/ mm^3, patients may receive, e.g. oral colistin sulfate (100.000E/kg, max. 4.000.000 E) optional as per local guidelines.

4.9.2. Prevention of GvH reaction / infection through blood transfusions

Transfusions of packed red cells or platelets should be leukocyte-depleted and irradiated with 30 Gy.

4.9.3. Antifungal prophylaxis

During chemotherapy and radiotherapy patients may receive antifungal prophylaxis according to local recommendations.

4.10. ONCOLOGICAL EMERGENCIES

4.10.1. Large mediastinal tumour

For patients with large mediastinal tumour the level of respiratory insufficiency should be determined.

level 0: No respiratory insufficiency. No restriction of trachea or bronchi visible in X-ray and / or thorax CT. No venous congestion.

level 1: Clinically no signs of respiratory insufficiency but radiological restriction of trachea or bronchi.

level 2: Stridor and / or upper venous congestion (first sign among others headache).

level 3: Orthopnoea

Only in patients up to level 1 a lymph node biopsy under local anaesthesia or a minithoracotomy in general anaesthesia can be performed. Before surgery it should be discussed with the anaesthetist that the patient may need prolonged mechanical ventilation for 1 – 2 days until the tumour has shrunk during treatment. In all other cases before biopsy a pre-phase with Prednisone/prednisolone 30 – 60 mg / m2 (5 – 10 days) should be initiated.
A therapeutic pleura puncture should be performed under local anaesthesia in case of respiratory insufficiency caused by a large pleural effusion. The same applies to a clinically relevant pericardial effusion.

4.10.2. Tumour lysis syndrome

In the rare case of tumour lysis syndrome (in patients with hyperuricemia or patients with bulky disease) the following is recommended:

- Hyperhydration with a liquid volume of 3000 (up to 5000 ml/m^2; maximal 7000 ml) per day.
- For forced diuresis the infusion should contain 10 mg Furosemide /1000 ml. Every 6 hours fluid balance should be calculated and if needed Furosemide should be applied additionally.
- The initial infusion should not contain KCl (addition of KCl only in patients with hypokalaemia only under strict indication with in short-term electrolyte checks).
- Urine alkalinization is not recommended as increasing the pH will reduce the solubility of phosphate.
- Prophylactically all patients should receive Allopurinol. In case of hyperuricaemia Rasburicase (Fasturtec® or a comparable drug) may be considered.

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6. CHEMOTHERAPEUTIC DRUG MONOGRAPHS

6.1. CYCLOPHOSPHAMIDE

SECTION 1

Alternative names

- Cyclophospham
- Endoxana TM
- Cytoxan TM .

Mechanism of Action

Oxazaphosphorine alkylating agent. Cyclophosphamide is a prodrug which undergoes biotransformation primarily by hepatic P450 mixed function oxidases to 4-hydroxycyclophosphamide. This metabolite decomposes spontaneously to produce the bifunctional alkylating species phosphoramide mustard. Bi-functional alkylating agents are thought to exert their cytotoxicity by forming intra-stand and inter-strand DNA cross-links at the N7 position of guanine residues. The generation of phosphoramide mustard is accompanied by the production of the metabolite acrolein which is thought to be partially responsible for the dose-limiting urotoxic effects of the drug. Co-administration of the uroprotectactant agent mesna (Sodium mercaptoethane sulphonate) can help prevent urotoxicity.

Considerations prior to administration

- Concurrent acute urinary-tract infection.
- Urothelial damage following previous cytotoxic chemotherapy or pelvic irradiation.
- Full Blood Count
- Renal function
- Liver function

Adverse effects

Common

- Dose related nausea and vomiting
- Alopecia
- Chemical or haemorrhagic cystitis if administered without mesna or with inadequate hydration and micturition.

Occasional

- SIADH

Rare

Cardiotoxicity presenting as congestive cardiac failure, pericardial effusion and pericardial tamponade. Possible association with previous anthracycline therapy or mediastinal irradiation.

SECTION 2

Recommended routes
Intravenous

Administration
By slow bolus into established IV line or by intravenous infusion over 1 hour.
By IV infusion in Glucose 5%, Sodium chloride 0.9% or Glucose/saline.

Dose/schedule

In order to prevent urothelial toxicity, hydration and mesna are required, particularly with higher daily doses of the drug.

Hydration and mesna

The manufacturers recommend concurrent mesna administration at daily doses of cyclophosphamide in excess of 10 mg/kg. In paediatric clinical practice, mesna is not required until higher daily, or higher cumulative doses per course are exceeded, providing adequate hydration and micturition can be maintained.

Daily cyclophosphamide doses < 10mg/kg (< 300 mg / m^2)
No mesna required, maintain fluid intake, encourage frequent micturition.

Daily or total course cyclophosphamide dose 300 mg / m^2 to 1 g / m^2
No mesna required. Intravenous hydration with glucose/ saline solution at a rate of 3 l / m^2/ 24 hours commencing with the first cyclophosphamide dose and continuing for at least six hours after last cyclophosphamide dose.

Daily or total course cyclophosphamide dose > 1 g / m^2
Intravenous hydration with glucose/saline solution containing mesna at 120% (mg/mg) of the prescribed daily cyclophosphamide dose. Infuse this solution at a rate of 3 l / m^2 / 24 hours, commencing 3 hours before the first cyclophosphamide dose and continuing for a minimum of 12 hours after completion of the last cyclophosphamide infusion.

Interactions

Possible with previous or current exposure to hepatic enzyme inducing agents including phenytoin[2].
Concurrent dexamethasone treatment may increase cyclophosphamide metabolism[2]
Concurrent allopurinol administration may decrease cyclophosphamide metabolism[2]

SECTION 3

Dilution specification

Cyclophosphamide is reconstituted with Water for Injections BP to produce a final concentration of 20 mg/ml. At this concentration, absorptive losses onto glass, PVC and polypropylene are thought to be negligible [3,4]

Compatible with glucose 5%, Sodium chloride 0.9% and glucose/saline solutions

Stability

Cyclophosphamide appears to be chemically stable when stored at 4^{o}C. A large body of information exists on stability and compatibility's of cyclophosphamide in solution.[3,4]

Pharmacokinetics

The pharmacokinetics of cyclophosphamide are complex, and since the anti-tumour activity of the oxazaphosphorines rests with their metabolites, little information can be gained from the pharmacokinetics of the parent drug. In children, the plasma half-life of cyclophosphamide ranges from 2.15 to 8.15 hours. Urinary excretion of cyclophosphamide and its metabolites is largely complete within 24 hours of administration[1]. Plasma half-life, apparent volume of distribution and total body clearance increase with increasing dose. Daily administration of cyclophosphamide over 2-4 days results in auto-induction of metabolism but this cannot be demonstrated with repeated 3-weekly courses of the drug [2].

Pharmacodynamics

The role of individual metabolites in producing tumour responses is still not clear. In children, there is significant inter-patient variation in metabolism and pharmacokinetics [1,2.], but the clinical consequences of these variations remain unknown. No correlation between either total plasma alkylating activity or individual metabolite plasma AUC's and tumour response has been demonstrated.

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6.2 DACARBAZINE

SECTION 1

Alternative names

5-(3,3-dimethyl-1-trazeno)imidazole-4-carboxamide. (DTIC)

Mechanism of action

- Purine analogue, inhibits purine synthesis
- Atypical alkylator
- Methylates nucleic acids
- Requires metabolic activation

Considerations prior to administration

Dose modification required in hepatic or renal abnormality

Adverse effects

Early

Common
- Myelosupression
- GI upset (nausea and vomiting most common)

Occasional:
- Flu like syndrome

Rare
- Alopecia
- Cutaneous hypersensitivity
- Hepatotoxicity
- Hepatic vein thrombosis

Late

Common
None

Occasional
- Photosensitivity

Rare
- Carcinogenic
- Teratogenic

SECTION 2

Recommended route
Intravenous

Caution

Protect from light

Administration

Intravenous bolus or infusion
Intra arterial

Dose/schedule

Interactions

Half life increases when corynebacterium parvum immunotherapy used
Interleukin-2 has been reported to increase the clearance of Dacarbazine[2].

Overdose

No recommendations

SECTION 3

Dilution specification and stability[6]

Dilute 100mg or 200 mg vials in 9.9 or 19.7 ml sterile water respectively
May be diluted in up to 250 ml of dextrose 5% or sodium chloride 0.9%.

Pharmacokinetics

With conventional doses (2.65-6.85 mg/kg) the terminal half-life of DTIC is 41 min, with a volume of distribution of 0.6 l/kg and clearance of 0.9 lk/kg/h[3].
Half-life values of 0.2 and 2.0 hr have been reported following intravenous infusion of high dose (850-1980 mg/m^2) DTIC, with a volume of distribution of 0.4 l/kg. Clearance was 0.6 l/kg/h, with 11 to 63% of the dose recovered unchanged in the urine[1].
Oral absorption is slow and incomplete[4].

Pharmacodynamics

There are no data available, but activity may depend upon metabolism[5].

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6.3 DOXORUBICIN

SECTION ONE

Alternative Names

Adriamycin hydrochloride,
14- hydroxydaunorubicin
3- Hydroxyacetyldaunorubicin [1]

Mechanism of action

Doxorubicin is an anthracycline antibiotic active in all phases of the cell cycle with maximal activity in S phase. It has several modes of action including intercalation to DNA double helix, topoisomerase II mediated DNA damage, production of oxygen- free radicals which cause damage to DNA and cell membranes, and complex formation with iron or copper via the hydroquinone moieties [2]. Iron doxorubicin complexes may contribute to cardiotoxicity by toxic free radical generation [3].

Considerations prior to administration

Well established robust venous access. A central venous catheter or indwelling vascular access port is recommended for prolonged infusions to reduce the risk of extravasation [2] .
Full blood count
Liver function tests
Cardiac function
Creatinine, urea, electrolytes

Adverse effects

Common
- Nausea and Vomiting
- Myelosuppression
- Alopecia
- Mucositis
- Red urine
- Diarrhoea
- Severe tissue damage if extravasated

Occasional
- Increased bilirubin
- Cardiomyopathy

Rare

- Hepatocellular necrosis
- Hyperpigmentation of skin, mucous membranes, nails
- Anaphylaxis, chills, fever
- Renal damage
- Drowsiness
- Conjunctivitis

SECTION TWO

Recommended routes
Intravenous

CAUTION
A baseline echocardiogram must be done prior to treatment. This should be repeated prior to alternate courses of doxorubicin up to a total cumulative dose of 300mg/m2 , and before each
course thereafter [4,5] . If the left ventricular shortening fraction (SF) is < 29% to 30% (depending on precise echocardiographic methodology [4,5]) temporary withdrawal of doxorubicin therapy should be considered [5]. If subsequent testing shows an improvement in SF consider reintroducing doxorubicin. A fall in SF by an absolute value of > 10 percentile units, or a rate of fall of > 2 to 3 percentile units per 100mg/m2, despite an SF > 29% to 30%, may also represent significant deterioration [5,6]. If the patients hepatic function is significantly impaired, doxorubicin dosage reduction should be considered [7,8,33,35] .

Dose /schedule

Due to the vesicant properties of doxorubicin it is strongly recommended that doxorubicin is given through a central venous line. For ease of administration, to reduce cardiotoxicity, and allow haematological recovery the following schedule is recommended:
administration of doxorubicin as a 6 hour infusion (in dextrose 5% or sodium chloride 0.9%)[9,10] .
Aministration as a single daily dose or divided doses fractionated over several days [7.]
Cmulative dose of 450mg/m2 to 550mg/m2, exceeded with extreme caution [7].

Intra-arterial administration has been investigated [7].

Interactions

Doxorubicin may interact with the following:-

- ICRF-187(Dexrazone)- reduce cardiotoxicity [11,12]
- Cardiac irradiation - increased cardiac damage
- Actinomycin, mithramycin- cardiomyopathy [13]
- Mercaptopurine- increased hepatotoxicity [13]
- Mitomycin-increased incidence of late congestive heart failure[13]
- Barbiturates - increased doxorubicin elimination [2,13]
- Verapamil- increased doxorubicin serum levels, reversal of doxorubicin resistance, reduced absorption of verapamil [2,13]
- Propranolol- increased cardiotoxicity [2,13]
- Tamoxifen- reduced doxorubicin clearance, modulation of doxorubicin resistance [2,13]
- Cyclosporin- increased doxorubicin serum levels and myelotoxicity, modulation of doxorubicin resistance [2,13]
- Carbamazepine, phenytoin, sodium valproate- altered anticonvulsant serum levels [13]
- Warfarin- increased warfarin effect [2,13]

- Cimetidine, ranitidine- increased doxorubicin toxicity [2]
- Interferon alfa-altered doxorubicin disposition, doxorubicin dose reduction [2]
- Paclitaxel-increased toxicity of doxorubicin, if administered after paclitaxel [32]
- Cyclophosphamide - increases AUC and reduces clearance of parent drug and active metabolite [38]

The clinical relevance of many of these interactions is unclear.

Overdose

Doxorubicin overdosage can prove fatal. Manifestations of overdose may include acute myocardial degeneration, severe myelosuppression and delayed cardiac failure. There is no specific antidote. Symptomatic supportive measures should be implemented [7,8.]

SECTION THREE

Dilution specification

Preparation

Doxorubicin supplied in :-

(i) Vials containing 10mg and 50mg freeze dried powder. Reconstitute with water for injection or sodium chloride 0.9% injection adding 5ml to the 10mg vial and 25ml to the 50mg vial to give a 2mg/ml solution [7,8.]

(ii) Vials containing 10mg and 50mg as a 2mg/ml solution in sodium chloride 0.9% [14.]

Dilution

Doxorubicin is compatible with sodium chloride 0.9% and dextrose 5% [7,8,14.]

Stability

A large body of information is available on the stability of doxorubicin in solution [15.] Doxorubicin is compatible with polypropylene [15,16,] polyvinyl chloride (PVC) [15,16] glass [17,] ethylene vinylacetate (EVA)[18] and polyisoprene [19] containers. Solutions should be protected from light during storage and administration unless the solution is freshly prepared and the concentration is greater than or equal to 0.5mg/ml [20.] In addition [15]. Doxorubicin appears to be chemically stable in polypropylene, PVC, or EVA containers for at least 7 days, when refrigerated or stored at room temperature, protected from light, and diluted in the following:

sodium chloride 0.9% at concentrations of 0.1mg/ml to 2mg/ml [16,18-23] : dextrose 5% at concentrations of 0.1mg/ml to 1.25mg/ml adsorptive losses which may be pronounced at low concentrations can be prevented by storage in polypropylene [16] or when doxorubicin is used at concentrations of at least 0.5mg/ml [16,18,24]. In addition, at least a 7 day expiry can be given to doxorubicin reconstituted with water for injection to a concentration of 2mg/ml, stored in polypropylene syringes at 4oC [16.]

Pharmacokinetics

The pharmacokinetics of doxorubicin in paediatric patients have been characterised in children, but the large number of protocols and different disease types make it difficult to produce representative summaries. Volume of distribution varies from 20-28 l/kg (approx. 609 l/m2) [33]. Anthracyclines are ionised and have low lipid solubility and so do not easily cross the blood-brain barrier. Doxorubicin is metabolised to doxorubicinol, an active metabolite which may occur at higher concentrations than parent drug in plasma [33]. Excretion of drug and metabolites is via further metabolism and/or biliary excretion, with only 5 to 15% excreted by the kidney [33]. Elimination is triphasic, with no effect of age on clearance when normalised for surface area [33]. Terminal half-life is 14 to 50 hours, with clearance varying from 267 to 1443 ml/min/m2 [33]. Relatively little difference in pharmacokinetics has been observed in infants, but there was a trend to lower systemic clearance than in older children (790 vs. 1500 ml/min/m2, p=0.07)[34]. Dosage adjustment has been recommended in patients with impaired hepatic function [33,35], although this has not been validated in paediatric patients.

Pharmacodynamics

Although some data exists regarding the influence of plasma concentrations on the therapeutic and toxic effects of doxorubicin, little of this has been obtained in paediatric patients [33,36,37].

Additional Information

A number of ways to reduce cardiotoxicity have been suggested but the use of an alternative dosage schedule of weekly rather than 3 weekly [25,26], prolonged infusion schedules [9,10,27-29], adjuvant cardioprotective agents (e.g. ICRF-187) [11,12] or the administration of doxorubicin in a liposome formulation [30], whilst increasingly advocated are not yet of proven utility.
The dose/schedule in this document is recommended as a reasonable compromise.
Due to the risk of cardiac abnormalities developing many years after doxorubicin therapy, long term cardiac follow up is recommended [31,39].

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6.4. ETOPOSIDE

SECTION ONE

Alternative names
- VP16
- VEPESID

Mechanisms of action:
Acts by inhibition of Topoisomerase II which results in DNA strand breakage

Considerations prior to administration
- FBC
- Renal function
- Liver function

Adverse Effects[1]
Common
- Alopecia
- Myelosuppression

Occasional
- Nausea/vomiting

Rare
- Anaphylactic reactions
- Fever
- Hypotensive reactions
- Headache
- Pruritus
- Pigmentation
- Mucositis
- Second tumours

SECTION TWO

Recommended routes

1) Intravenous

Administration

- Ampoules 100mg in 5ml
- Dilute to a concentration of 0.4mg/ml in 0.9% Sodium Chloride Injection, give as an IV infusion over 1 to 4 hours[2]. One hour infusion is recommended in order to avoid problems with “line time” during complex chemotherapy regimens.

- Data sheet recommends administration over at least 30 minutes, to avoid hypotensive reaction.[3]
- Due to potential solubility problems care should be taken when mixing with other agents[2].

Dose/schedule

Daily administration has greater anti-tumour efficacy than an equivalent dose given over 24 hours with comparable toxicity + AUC e.g. 100mg/m^2/day for 5 days versus 500mg/m^2 over 24 hours[5,6], although this is the subject of some debate[7].
Drug is undetectable (< 0.2microgram/ml) in plasma by 48 hours post administration in the majority of patients (important for protocols with marrow reinfusion)[8].

2) Oral

- Gelatin capsules 100mg and 50mg
- Injection can be used orally 20mg/ml (5ml amp)

Administration

- Short elimination $t_{½}$ suggests twice daily dose
- Prolonged administration is possible but careful monitoring of haematological toxicity is necessary

Interactions (IV and Oral preparations)

- No major interactions with the possible exception of warfarin, where etoposide may displace protein bound warfarin or alter it's metabolism, leading to increased prothrombin times[1,9]
- Cisplatin may reduce the clearance of etoposide[10].
- For the related drug tenopiside and possibly for etoposide as well, co-administration of anticonvulsants (Phenytoin or Phenobarbitone) can also result in increase clearance[9].

Overdosage (IV and Oral preparations)

- Full supportive measures, including the use of growth factors should be considered.
- Dialysis and haemofiltration are not effective as etoposide is highly plasma protein bound[11].

SECTION THREE

Dilution specification & stability
Intravenous

- Manufacturers recommend diluting to 0.25mg/ml, however a dilution of 0.4mg/ml is stable at room temperature for 96 hours (may precipitate if refrigerated).
- Only licensed in UK for administration in Normal Saline.
- Poor water solubility therefore formulated in polyethylene glycol solubilising agent which dissolves plastics.
- Use nylon filters + PVC bags or glass bottles

Oral

- IV preparation is stable for 28 days in glass vials.

Pharmacokinetics:

Intravenous

- Medium (range) clearance 26 (14-54) ml/min/m^2, $t_{1/2B}$ 132 (87-673) mins [8,12,13].
- AUC - 3.9 (1.8 - 7.3)mg/ml.min/100mg/m^2.

- Children tend to have shorter elimination half life than adults, possibly because of better renal function and hence higher renal clearance. Clearance can be increased in hypoalbuminaemic patients leading to a reduced AUC. However, since this is associated with a reduction in protein binding, haematologic toxicity may be greater in such patients[14].
- Clearance is independent of age[8,15] and dose[8] (90 - 25Omg/m^2) but is more variable at doses > 100mg/m^2 and therapeutic drug monitoring may be indicated.

Oral

- Absorption of capsules differs from IV preparation taken orally[9].
- Approximate equivalence ratios:

IV: Oral capsules	1:2
IV: Oral injection	1:1.4
Oral capsules: Oral injections	1:0.7

- Larger oral doses over 200mg/m^2 are less effectively absorbed than lower doses.
- Medium bioavailability is 48% at dose > 300mg, but 86% at a dose of 100mg. This suggests a saturable step in oral absorption[16].
- Oral bioavailability varies, with big inter and intra patient variability[17,18].
- Bioavailability is not affected by food.

Pharmacodynamics:

Correlation's between AUC and/or- steady state levels and haematological toxicity has been seen in adult patients[19]. There is a closer pharmacodynamic relationship with unbound rather than with total concentrations of etoposide in plasma[20,21].

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6.5. VINBLASTINE

SECTION ONE

Alternative names:
- Velbe

Mechanisms of Action
Tubulin binding agent producing mitotic arrest.

Considerations prior toadministration

Ensure good, robust, venous access
Hepatic function.

Adverse effects

Common
- Abdominal pain
- Constipation
- Leucopenia

Occasional
- Peripheral neuropathy (mild)
- Thrombocytopenia and Anaemia

Rare
- Nausea and vomiting
- Alopecia
- Paralytic ileus

SECTION TWO

Recommended routes

By bolus injection or into the tubing of a fast running intravenous infusion.
Hydration not required.

CAUTION

Vinblastine is a highly vesicant drug, and great care must be taken to avoid extravasation

Dose/schedule

Concentration for administration 1 mg/ml.
Recommended dose: 6mg/m^2 no more frequently than every 7 days.
Maximum dose: 10mg.

Interactions
Nil known

SECTION THREE
Pharmacokinetics:

There are no published data on the clinical pharmacokinetics of vinblastine in children. In adults, vinblastine plasma clearance is greater than that of vincristine, possibly explaining the need to administer higher doses of vinblastine[1] . In adults, vinblastine pharmacokinetics are variable and elimination is due to metabolism, urinary and faecal excretion[1] . Daily administration in adults can lead to vinblastine accumulation[2] . Vinblastine pharmacokinetics may be non-linear and dependent upon hepatic function[3] . A dose reduction has been recommended for patients with a raised serum bilirubin [4].

Pharmacodynamics

Unconfirmed studies in adults suggest that patients treated with continuous infusion vinblastine are more likely to develop leucopenia if plasma levels exceed 1ng/ml,[5] and that reduced clearance may also be associated with an improved response rate in breast cancer [6].

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K Lu et al

6.6. VINCRISTINE

SECTION ONE

Alternative names
- Oncovin

Mechanisms of action

Tubulin binding agent producing mitotic arrest.

Considerations prior to administration

- Well established, robust, venous access.
- Hepatic function.
- Neurotoxicity
- Avoid administration at the same time as intrathecal methotrexate.

Adverse effects

Common
- Alopecia
- Abdominal pain - cramps
- Pain in jaw, bones and joints
- Constipation

Occasional
- Peripheral neuropathy (loss of deep tendon reflexes)
- Autonomic neuropathy (paralytic ileus, urinary retention)

Rare
- Leucopenia, Thrombocytopenia, Anaemia
- Nausea and vomiting
- Raised LFTs (mild and transient)
- Convulsions
- Diplopia and Photophobia

Toxicity related to individual and cumulative dose of Vincristine

SECTION TWO

Recommended routes

By bolus injection or into the tubing of a fast-running intravenous infusion.
Hydration not required.

CAUTION
Vincristine is a highly vesicant drug, and great care must be taken to avoid extravasation.

DO NOT GIVE INTRATHECALLY

Dose /schedule

- Variable
- Dose reduction may be necessary if toxicity unacceptable
- The need to limit the total vincristine dose per administration to 2mg is not supported by clinical experience in adults.[1]

Interactions

Vincristine plasma clearance can be reduced by nifedipine[2], cimetidine[3] or ranitidine[3], and increased by phenobarbitone[3]. The clinical relevance of these interactions in not clear.

Overdose

Plasmapheresis and phenobarbitone have been reported to be of value in cases of systemic vincristine overdose[4,5].

SECTION THREE

Dilution specification

- Dextrose 5%, Sodium Chloride 0.9%
- Undiluted at 1 mg/ml but at this concentration there would be increased toxicity with extravasation, therefore can be administered at lower concentrations, e.g. 0.2 mg/ml.

Stability

- Solution 1 mg/ml - 2 years in vial at 2 to 8 ^{o}C
- Lyophilised powder - 3 years at 2 to 8 ^{o}C. Chemically stable for 30 days after reconstitution when stored at 2 - 8 ^{o}C.

Pharmacokinetics

Vincristine is eliminated by hepatic metabolism and biliary excretion[6]. Clearance is variable and may be age dependent.[3,7]

Mean (±SD) pharmacokinetic parameters:[3,7]

Clearance	431±238, 482±342	ml/min/m^2
t½b	1122±1128, 823±390	min
AUC	3.2±1.8, 2.9±2.1	mg/ml.min *per* 1.4mg/m^2

In adults, but not children, vincristine neurotoxicity has been related to AUC[3,8]. Also in adults, impaired liver function has been related to reduced clearance and predisposition to neurotoxicity[9]. A dose reduction has been recommended for patients with a raised serum bilirubin[10].

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5.1. 6.7. ABBREVIATIONS

ALAT	Alanine-amino-transferase
AML	Acute Myeloid Leukemia
AP	Alkaline Phosphatase
ASAT	Aspartate-amino-transferase
ASHAP	Chemotherapy cycle: Adriamycin, Methylprednisolone, Cytarabin, Cisplatinum
B-symptoms	Systemic symptoms: unexplained fever, weight loss, night sweats
C	Celsius
°C	Degree Celsius (temperature dimension unit)
Ca	Calcium
CCS	Children`s Cancer Study
CD	Compact Disc
cf.	Confer
Cm	Centimeter
CMV	Cytomegalovirus
CNS	Central Nervous System
COMP	Chemotherapy cycle: Cyclophosphamide, Vincristine, Methotrexate, Prednisone

COPDAC	Chemotherapy cycle: Cyclophosphamide, Vincristine, Prednisone, Dacarbazine
COPP	Chemotherapy cycle: Cyclophosphamide, Vincristine, Prednisone, Procarbazine
Cp	compare
CR	Complete remission
Cru	Complete remission unconfirmed
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
Cum.	cumulative
CV	Curriculum Vitae
D	Dimension
2D	Two-dimensional
3D	Three-dimensional
DAL	Deutsch-OEsterreichische-Leukaemie/Lymphom-Liga
DAL-HD	Deutsch-OEsterreichische-Leukaemie/Lymphom-Liga-Hodgkin`s Disease
DD	Differential diagnosis
DFS	Disease free survival
DICOM	Digital imaging file format
DNA	Desoxyribonucleic acid
DTIC	Dacarbazine
DVH	Dose Volume Histogram
EBV	Epstein Barr Virus
ECG	Electrocardiogramme
Echo	Echocardiogramme
Echo-CG	Echocardiogramme
ED	Einzeldosis (single dose)
EEG	Electroencephalogramme
EFS	Event free survival
e.g.	Example given
E-lesions	Extranodal lesions by contiguous involvement
ENT	Ear, Nose and Throat
Et al.	Et altra (and others)
Euro-Net-PHL-C1	European Network on Pediatric Hodgkin`s Lymphoma-Classical Hodgkin-1
FAB	French-American British (classification for acute leukemias)
FFTF	Freedom from treatment failure
FF2F	Freedom from second failure
Fig.	Figure
FSH	Follicle stimulating hormone
GGT	Gamma Glutamyl transferase

GOT	Synonyme for ASAT (Aspartate-amino-transferase)
GPOH	Gesellschaft fuer Paediatrische Onkologie und Haematologie, (German Society for Paediatric Oncology and Haematology)
GPOH-HD	GPOH-HodgkinStudiengruppe (GPOH-Hodgkin`s study group)
GPT	Synonyme for ALAT (Alanine-amino-transferase)
Gy	Gray
h	Hour
HCV	Hepatitis C Virus
HIV	Humane Immunodeficiency Virus
HL	Hodgkin`s Lymphoma
HLA	Human Leukocyte Antigen
HSV	Herpes simplex virus
5-HT-3 antagonist	Serotonine-antagonist
ICH	International Conference on Harmonisation
ID	Identification code
i.e.	Id est
IF-RT	Involved field radiotherapy
Incl.	Including
i.v.	intravenously
KCL	Potassium chlorine
Kg	Kilogram
LDH	Lactate dehydrogenase
LH	Luteinizing Hormone
LH-RH	Luteinizing Hormone Releasing Hormone
LN	Lymph node
m²	Square meter
mAS	milli Ampere seconds
mg	Milligram
min	Minimum
ml	Milliliter
mm	Millimeter
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NC	No change
NCI	National cancer institute
NCR	No carbon required
ND	Not done
NHL	Non Hodgkin’s lymphoma
Non-GPOH	Not belonging to GPOH group
OEPA	Chemotherapy cycle: Vincristine, Etoposide, Prednisone, Adriamycine
OE*PA	Chemotherapy cycle: Vincristine, Etoposide (20% increased dose),

	Prednisone, Adriamycine
OPA-COMP	Chemotherapy cycle: Vincristine, Prednisone, Adriamycine - Cyclophosphamide, Vincristine, Methotrexate, Prednisone
OPPA	Chemotherapy cycle: Vincristine, Procarbazine, Prednisone, Adriamycine
OPPA_COPP	Chemotherapy cycle: consisting of OPPA and COPP
OS	Overall survival
PCR	Polymerase Chain Reaction
PD	Progressive disease
PFS	Progression free survival
p.i.	Per injectionem
p.o.	Per os (by mouth)
PP	Per-protocol
PR	Partial remission
Prog.	Progression
11q23	Cytogenetic abnormality; fusion chromosome
Resp.	Respective(ly)
RG	Response group
RIF	
RNA	Ribonucleic acid
SD	Standard deviation
SE	Standard error
SIAD	Syndrome of inadequate
SmPC	Summary of medicinal Product Characteristics
Sono	Sonography, ultrasound
SOP	Standard Operating Procedures
SST	Secondary solid tumour
T2-STIR	Fat saturated T2-weighted spin echo sequence (MRI)
T1-Flash	T1-weighted gradient echo sequence (MRI)
TG	Therapy group
T2-TIRM	Fat saturated T2-weighted spin echo sequence (MRI)
TOX	Toxicity
T1-SE	T1-weighted spin echo sequence (MRI)
TSH	Thyroid stimulating hormone
TTT	Therapy titration study
VCR	Vincristine
VP-16	Etoposide
Vs.	versus
WHO	World Health Organisation
VZV	Varicella zoster Virus
X-ray	Two-dimensional radiogramme