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the European Society for Paediatric Oncology

EuroNet-PHL

European Network for Pediatric Hodgkin Lymphoma

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

STANDARD CLINICAL PRACTICE RECOMMENDATIONS FOR PAEDIATRIC HODGKIN LYMPHOMA (PHL) FIRST-LINE TREATMENT OF CLASSICAL HL

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EuroNet-PHL-C1 and -C2 Trials
EuroNet-PHL Group Treatment Recommendations after closure of EuroNet-PHL-C2
Treatment recommendations of the GPOH-HD Study Group_Version2.0

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1. BACKGROUND AND RATIONALE

1.1 Background and Rationale

EuroNet-PHL-Standard Clinical Practice Document is a comprehensive treatment strategy for all first line classical Hodgkin Lymphoma (cHL) patients under 18 years and up to under 25 years in countries that treat young adult cancer patients in paediatric or AYA settings.

The document is an extension of the EuroNet-PHL-C2 trial strategy with the adaptation of the EuroNet-PHL Clinical Board recommendations.

The EuroNet-PHL Clinical Board established the current recommendations at the meeting held in Paris (January, 13-14 2023) after review of the 5th formal interim analysis of the EuroNet-PHL-C2 trial.

The data of EuroNet-PHL-C2 are mature but not yet published. Therefore, results must still be considered preliminary. The data analysis will continue and the present recommendations will be updated as required.

These recommendations take into account the actual outcome, the toxicity profile, and, for children and adolescents with inadequate response at early response assessment (ERA), the burden of radiotherapy (RT).

The overall strategy is risk stratified, defining the required chemotherapy and response adapted, defining the radiotherapy burden to tailor the amount of treatment to the individual patient. With this strategy long term complications shall be decreased or eliminated

- Radiotherapy indication will be restricted.

Patients with a negative PET scan after two cycles of OEPA chemotherapy will not receive radiotherapy. The threshold for negative PET scan at ERA (early response assessment) shifts from the previously used Deauville 1 and 2 as negative to Deauville 1, 2 and 3 as negative, thereby increasing the number of negative patients without indication for RT.

- Chemotherapy Randomisation

All intermediate (TL-2) and advanced stage (TL-3) patients had been randomised between respectively 2 or 4 standard COPDAC-28 or intensified DECOPDAC-21 consolidation chemotherapy cycles. Therefore, two randomised sub-studies had been performed based on the ERA-PET response:

Patients with adequate response at ERA do not receive radiotherapy - a randomised controlled chemotherapy comparison to show that intensified DECOPDAC-21 consolidation chemotherapy improves EFS as compared to standard COPDAC-28

Patients with inadequate response at ERA - a randomised controlled chemotherapy-radiotherapy comparison - to show that DECOPDAC-21 combined with radiotherapy restricted to sites that remain FDG-PET positive at the end of all chemotherapy (Late response assessment – LRA) has comparable EFS compared to COPDAC-28 plus standard involved node radiotherapy as in the C1 trial.

- Refined Risk stratification

Former treatment groups (TG) of the EuroNet-PHL-C1 trial are reassigned into treatment levels (TL) by shifting early-stage patients (former TG-1) with risk factors into TL-2.

- Semi-quantitative ‘qPET’

Results of semi-quantitative qPET had been used in the central review for response assessment

Brief summary of EuroNet-PHL-C2 results

In 2.881 patients treatment levels (TLs) have been assigned. The distribution of the study population is → TL-1: 15.5%, TL-2: 41.3%, TL-3: 43.2%.

Overall, EuroNet-PHL-C2 results are good: overall EFS at 3 years is > 90% and overall OS is > 99%.

There is no warning sign for any subgroup neither for outcome nor for acute toxicity.

Comparison with the recently published [1, 2] EuroNet-PHL-C1 results, highlights some differences:

1) The outcome is significantly different according to the treatment level (TL-1 > TL-2 > TL-3). Of note, within TL-2, patients formerly classified in TG-1 with risk factors (ESR > 30 and/or bulk > 200 ml), e.g. the previous "TG-1 High Risk" group, have the same outcome than other TL-2 patients

2) The outcome is significantly different according to ERA status (AR or IR). This was not the case in C1. To be reminded: in C1 the adequate response at ERA (ERA-AR) was defined by DS1 to 2, and RT was given with the same modalities in both arms e.g. COPP and COPDAC.

Results according to treatment level and ERA PET status:

TL-1:

Results are excellent without difference between AR and IR

TL-2 and TL-3:

1) Patients in AR:

Preliminary results suggest that DECOPDAC-21 arm will be associated with slightly better 3-yr-EFS than the COPDAC-28 arm. Results are similar for patients with ERA DS1-2 and patients with ERA DS3. No other prognostic factor study is available for this subgroup.

2) Patients in IR:

DECOPDAC-21 with late response assessment-(LRA) adapted involved node radiotherapy (IN-RT) is similar or slightly below (~ 3%) in EFS than COPDAC-28 + IF-RT +/- LRA-defined boost.

Still, ERA-IR patients will encounter a high burden of radiotherapy (RT) in the standard arm. The use of DECOPDAC-21+/- INRT arm is associated with a marked reduction of radiotherapy indication, and for those who will actually receive INRT, with a significant reduction of RT fields. For TL-2 ERA-IR patients, the rate of RT in children treated with DECOPDAC-21 is reduced by a factor of 2, and for TL-3 ERA-IR patients by a factor of 3 compared to the IR Results in C1.

Of note, DECOPDAC-21 appears to be more effective than COPDAC-28 in converting ERA DS5+ into LRA_AR but there is no benefit in outcome (EFS). However, this will hopefully translate in less late toxicity of RT in these patients.

Table 1: Radiotherapy indication in the full analysis set of n= 2691 EuroNet-PHL-C2 patients

Ntotal=2691	TL-1	%col.1	TL-2	%col.2	TL-3	%col.3	All	%All
AR	385	87.1	809	73.3	636	55.5	1830	68
IR	57	12.9	294	26.7	510	44.5	861	32
Nvalid	442	100	1103	100	1146	100	2691	100

*Distribution of AR (no radiotherapy) and IR (Radiotherapy indication) patients by the TLs (treatment levels) of all patients in the full analysis set. Only **32%** overall had a radiotherapy indication according to overall response at end of treatment.*

Table 2: Radiotherapy indication in the full analysis set and in the different consolidation arms of n= 2689 of EuroNet-PHL-C2 patients

Ntotal=2689	TL1	%col.1	TL2-C	%col.2	TL2-D	%col.3	TL3-C	%col.4	TL3-D	%col.5	All	%All
noRT	386	87.1	412	75.2	492	88.6	310	54.1	489	85.8	2089	77.7
RT	57	12.9	136	24.8	63	11.4	263	45.9	81	14.2	600	22.3
Nvalid	443	100	548	100	555	100	573	100	570	100	2689	100

*Distribution of noRT (no radiotherapy) and RT (Radiotherapy indication) patients by the TLs (treatment levels) of all patients in the full analysis set. In TL-2 and TL-3 both, the COPDAC-28 arm (C) and the DECOPDAC-21 arm (D) are displayed. Only **11.4%** in D-TL-2 and **14.2 %** in D-TL-3 had a radiotherapy indication (in D-arms only INRT but 30Gy SD to remaining PET+-ve sites) according to overall response at end of treatment.*

Other data of interest:

1) Acute toxicity in COPDAC-28 and DECOPDAC-21 arms:

The DECOPDAC-21 arm is associated with significantly higher rates of hematological toxicity (CTCAE grades 3 + 4), especially for CTCAE grade 4 neutropenia, in comparison to the COPDAC-28 arm. Nevertheless, CTCAE grade 4 infections are rare (<1% per cycle in DECOPDAC-21).

Non-hematological > grade 3 toxicities are rare in both arms: gastrointestinal (diarrhea, vomiting, stomatitis) < 1% per cycle, and hepatic (elevated liver enzymes) < 5% per cycle. There was no toxic death in the randomized consolidation phase in the EuroNet-PHL-C2 study.

2) Cumulative doses of chemotherapy (Table 3)

doses (mg/m²)	TL-2 COPDAC-28	TL-2 DECOPDAC-21	TL-3 COPDAC-28	TL-3 DECOPDAC-21
Doxorubicine	160	210	160	260
Etoposide	1,250	1,850	1,250	2,450
Dacarbazine	1,500	1,500	3,000	3,000
Cyclophosphamide	2,000	2,500	4,000	5,000
Prednisone/-olone	1,200 (capped at 2400mg)	640	2,400 (capped at 4800mg)	1,280

2. PATIENT GROUP

EuroNet-PHL-C2 is a comprehensive treatment strategy for all first line classical Hodgkin Lymphoma (cHL) patients under 18 years and in countries with dedicated AYA treatment units for up to under 25 years.

2.1 Diagnostic Criteria

2.1.1 Imaging:

For Staging and response assessment, cross-sectional imaging combined with PET (i.e. PET-CT and or PET-MRI) are strongly recommended. For assessment of parenchymatous organs like spleen and liver, abdominal ultrasound is recommended in addition. The imaging procedures and requirements are detailed within the appendix 2 “Screening Procedures”.

2.1.1. Assessment of Involvement

Assessment of Lymphatic Involvement

Lymph node involvement

- If the largest diameter of a lymph node or a lymph node conglomerate is smaller than 1 cm the region is considered not involved – independent of the PET result. Small tumour lesions do not impair therapy results according to previous experience.
- If a lymph node or a lymph node conglomerate has a diameter of 1.0 – 2.0 cm the region is considered involved only if it is FDG-PET positive.
- If the largest diameter of a lymph node or a lymph node conglomerate exceeds 2.0 cm the region is considered involved – independent of the PET result.

Definition of bulk

Bulk is present if the volume of the largest contiguous lymph node mass is ≥ 200 ml. In the mediastinum the total volume of the initial tumour mass in the upper, middle and lower mediastinum and both hila and both supradiaphragmatic recessus is considered contiguous for bulk assessment due to the complex anatomic structure.

Volumes will be measured using the three largest perpendicular diameters on multiplanar reconstruction mode in CT/MRI (Bulk volume calculation = A x B x C/2 = > 200 ml)

Assessment of Waldeyer’s ring

Involvement is defined by clinical assessment preferably by an ENT physician.

Biopsy is not recommended.

(At ERA reassessment of Waldeyer`s ring is not used for definition of response groups.)

Spleen involvement

Spleen involvement is assumed if

- focal PET positive lesions that are confirmed by CT or MRI or ultrasound

or

- tumour suspicious multiple small focal changes in the spleen structure are detected by ultrasound – irrespective of the FDG-PET result.

Exclusive splenic involvement without other lymphatic disease is classified as stage I.

Assessment of E-lesions

An E-lesion is a contiguous infiltration of a lymph node mass into extra-lymphatic structures or organs (e.g. lung, bone).

Involvement of the pleura

Involvement of the pleura is assumed if

- an adjacent nodal lesion infiltrates the pleura or chest wall **AND**
- the infiltrate and/or the adjacent nodal lesion is PET positive

Pleural effusion is **not** considered to be an E-lesion**.**

Pericardial involvement

Pericardial involvement is assumed if

- an adjacent nodal lesion infiltrates the pericardium **AND**
- the infiltrate and/or the adjacent nodal lesion is PET positive

Pericardial effusion is **not** considered to be an E-lesion.

Organ Involvement

Disseminated organ involvement always implies stage IV.

Lung involvement

Disseminated lung involvement is assumed if

- there are more than two small foci between 2 mm and 10 mm within the whole lung

  or
- there is at least one intrapulmonary focus of a diameter ≥ 10 mm

If ***all*** lesions are exclusively in one lung, then only this particular lung is considered as involved. However, even if there is just **one additional** smaller focus found within the other lung, then both lungs are considered involved.

Liver involvement

Liver involvement is assumed if at least one focal PET positive lesion is confirmed by CT or MRI or ultrasound.

Skeletal involvement

- *Bone marrow* involvement is assumed, if
  - More than two PET-positive lesions are found in skeleton, irrespective of positivity in CT or MRI

- *Bone* involvement is assumed, if
    - the PET-positive skeletal lesion shows tumour-typical correlation in CT (or increased uptake in bone scan)

NB Bone scan from head to toe is only carried out when PET techniques without CT (i.e. PET-MRI & PET alone) are used and there is no CT of the respective region

Note Bone Marrow Biopsy – is no longer a mandatory investigation as bone marrow involvement is defined by the FDG PET scan.

2.1.2. Stage Classification

Stage classification is performed according to Cotswolds revision of the Ann Arbor staging system.

Independent Lymph Node Regions

Independent lymph node regions are:

- **Waldeyer's ring (left and right)**
- **cervical (left and right) with sub-regions relevant for irradiation:**
    - upper neck: above hyoid bone
    - lower neck: below hyoid bone above lower margin of cricoid cartilage
- **supraclavicular (left and right)** (below lower margin of cricoid cartilage above fossa jugularis
- **infraclaviular (left and right)**: (subpectoral on the thoracic wall)
- **axillar (left and right)**
- **pulmonary hilum (left and right):** bronchopulmonary lymph nodes
- **mediastinum with sub-regions relevant for irradiation:**
    - upper mediastinum: fossa jugularis to carina, including paratracheal and paraoesophageal lymph nodes, preaortic lymph nodes and lymph nodes in the aorto-pulmonary window, trachea-bronchial lymph nodes
    - lower mediastinum: lymph nodes clearly below carina to upper edge of the diaphragm along the oesophagus, the lower descending thoracic aorta and spine
    - Mammaria interna (left and right)
    - **supradiaphragmatic recessus** (below upper edge of the diaphragm but still above diaphragm)
- **spleen**
- **splenic hilum**
- **porta hepatis**

- **mesenteric:** mesentery or mesocolon
- **paraaortic:**
- upper (above the renal hilum),
- lower (at or below the renal hilum)
- **iliac (left and right):** below aortic bifurcation to inguinal ligament
- **inguinal (left and right):** below inguinal ligament

Stage Classification of Hodgkin 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 two 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

Additional Stage Definitions

A No B symptoms

B At least one of the following systemic symptoms

a. Unexplained 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 to known nodal site

2.1.3. Treatment Levels and Allocation

Patients are assigned to treatment levels (TL) according to stage, bulk and ESR values (see Fig. 16). Treatment levels are defined as follows:

TL-1:	stage IA/IB/IIA with ESR < 30 and without bulk
TL-2:	stage IA/IB/IIA with missing ESR or ESR ≥ 30 or with bulk stage IAE/IBE/IIAE/IIB/IIIA
TL-3:	stage IIBE stage IIIAE stage IIIB stage IV

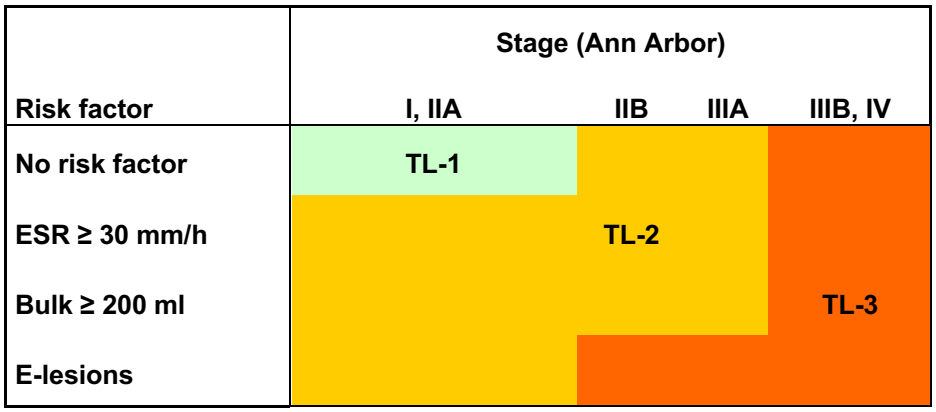


Figure 2: **Treatment levels (TL) according to stage, bulk, ESR and E-lesions**

2.2. Histopathology

The histo-pathological diagnosis is based on biopsy of lymph nodes or other primarily involved organs before treatment start. Biopsies should be excision or tru-cut biopsies where adequate diagnostic material is obtained. Fine needle aspiration biopsies are not appropriate. Pathology Review is preferable and should be carried out at initial diagnosis and relapse diagnosis. The local Investigator is responsible for ensuring that the correct materials (tissue and documentation) are submitted for to the appropriate Reference Pathologist immediately after treatment start.

2.3. Molecular pathology

The molecular pathology in pediatric Hodgkin lymphoma is not available as standard procedure in local sites anywhere in Europe but is performed in dedicated research programmes in collaborative studies and trials and at specialized reference laboratories. If your patient and parents agree to be included in these trials please contact the ERNPaedCan centre in Gießen, Germany.

For participation the following data and biomaterials need to be obtained before start of chemotherapy treatment:

- FFPE-lymphoma sample (will be returned after probe sampling)
- Sample (10 ml minimum) for liquid biopsy (=ctDNA), preferably in Streck or Qiagen tubes, dedicated for ctDNA sampling, do not freeze, do not store in refrigerator
- Serum and EDTA samples, minimum 10 ml each

- Informed consent to participate in dedicated trials can be obtained immediately after asservation of the biomaterials and after request of study outline from the ERNPaedCan centre in Gießen, Germany

3. TREATMENT DETAILS

3.1 Treatment

3.1.1.EuroNet-PHL group recommendations for the childhood and adolescent cancer centres

These recommendations are for children and adolescents with classical Hodgkin lymphoma treated in first line.

Physicians must be familiar with EuroNet-PHL C2 design and should refer to the whole protocol for any detail regarding staging, stratification, chemotherapy cycles, radiotherapy, and PET assessment.

Generally, treatment is allocated (as prescribed in the EuroNet-PHL-C2 protocol) ***according to TL-1, TL-2 or TL-3.***

Treatment Level 1 (TL-1)

All patients receive two cycles of OEPA.

Patients in TL-1 with a negative PET scan at ERA have an adequate response (AR) and receive one cycle of COPDAC-28. The third chemotherapy cycle (COPDAC-28) starts as soon as possible after confirmation of the negative PET result. Preferably, consolidation COPDAC-28 should start within **one week after ERA, within three weeks latest**.

Patients in TL-1 with a positive PET scan at ERA have an inadequate response (IR) and will receive involved node radiotherapy to all initially involved sites. Radiotherapy should start as soon as possible after decision on radiotherapy in the local MDT.

Follow-up visits start six weeks after completion of therapy (details see **3.6. Follow Up of Patients**).

Treatment Level 2 and 3 (TL-2 and TL-3)

All patients receive two cycles of OEPA, followed by two (TL-2) or four (TL-3) cycles of COPDAC-28 or DECOPDAC-21 consolidation treatment according to the respective recommendation, depending on response assessments (ERA or LRA); see below.

Patients in TL-2 and TL-3 with a negative PET scan at ERA (AR) receive no radiotherapy.

Patients with a positive PET scan at ERA (IR) will receive either COPDAC-28 chemotherapy and standard involved node radiotherapy to all initially involved sites and a boost to LRA PET-positive residuals or intensified DECOPDAC-21 chemotherapy and radiotherapy to LRA PET-positive sites with morphologic residuals only. Radiotherapy should start as soon as possible after decision on radiotherapy in the local MDT.

Initial staging : as in EuroNet-PHL-C2 (see chp. 2 of the present ESCP)

Stratification : as in EuroNet-PHL-C2 (see chp. 2 of the present ESCP)

Induction : as in EuroNet-PHL-C2: OEPA x 2 (see chp. 3 of the present ESCP)

ERA-PET : as in C2: according to the Deauville score (DS):

- Adequate response (AR) is DS1 to 3,
- Inadequate response (IR) is DS4 and 5

LRA-PET : as in C2: only in pts with IR at ERA; according to the DS:

- Adequate response (AR) is DS1 to 3,
- Inadequate response (IR) is DS4 and 5

Consolidation:

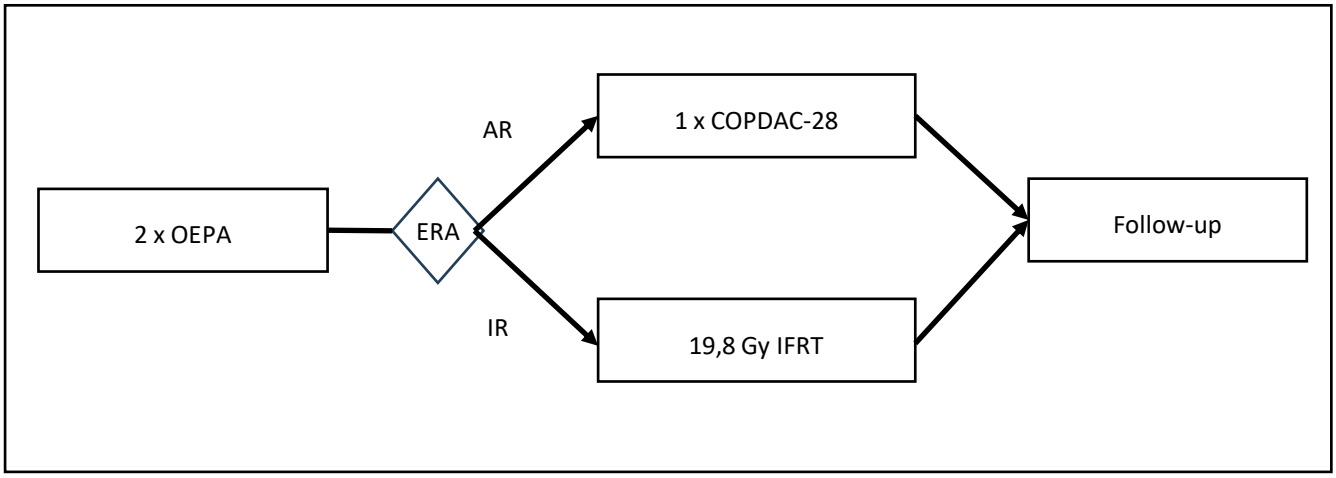
1) Patients with adequate response:

- TL-1: as in C2: OEPA X 2 and 1 cycle of COPDAC-28
- TL-2: Both C2 arms are valid options as the difference in EFS is limited. Treatment should be discussed with the patient and parents and with national representatives if required.
- TL-3: DECOPDAC-21 x 4 is the recommended arm (*exception: patients with contraindications against anthracyclins or etoposide*)

2) Patients with inadequate response:

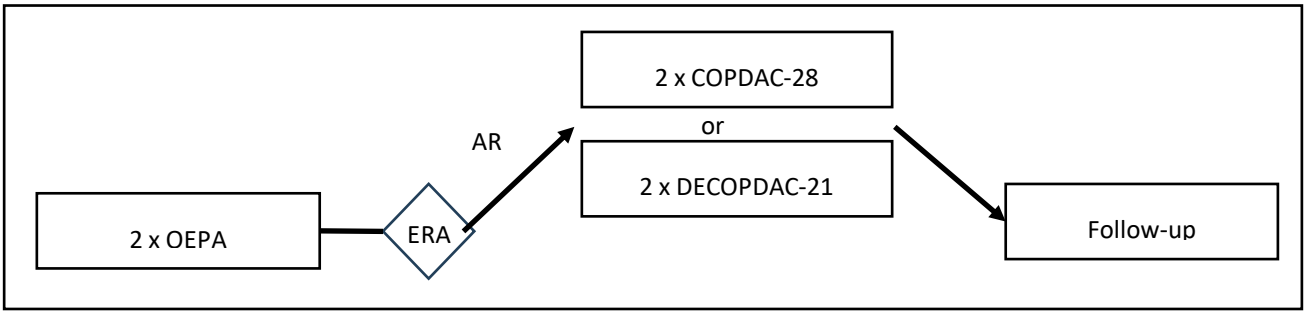
- TL-1: as in C2 with IFRT (photons or protons) like in C2
- TL-2: according to C2 DECOPDAC-21 arm
- TL-3: according to C2 DECOPDAC-21 arm.
- TL-2 and TL-3: Radiotherapy: indication, fields and boost according to LRA as in C2:
  - COPDAC-28 arm: RT on initially involved sites (19.8 Gy) + boost (10 Gy) on positive sites (DS4 and 5) at LRA
  - DECOPDAC-21 arm:
    - Patients in CMR (DS1 to 3) at LRA: no radiotherapy
    - Patients non in CMR at LRA: INRT on positive sites (DS4 and 5) at LRA (28.9 Gy), = Residual Node RT on PET-+-ve remaining sites (RNRT-PET^{+})

Recommendation for TL-1:

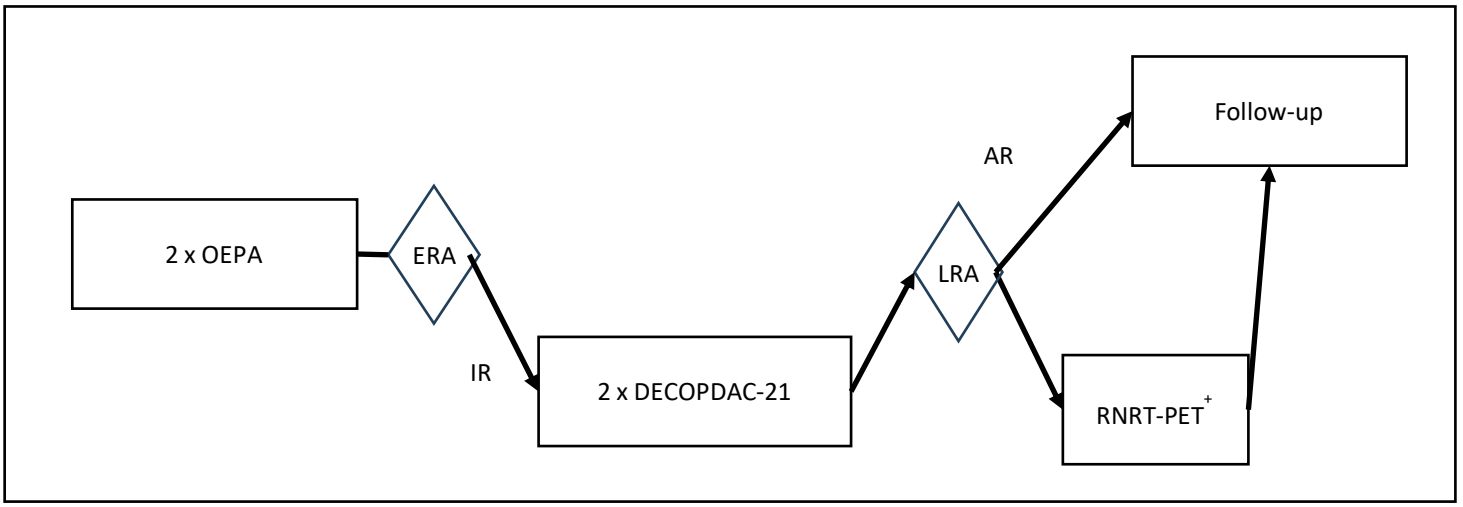


Recommendation for TL-2:

ERA-Adequate Responders

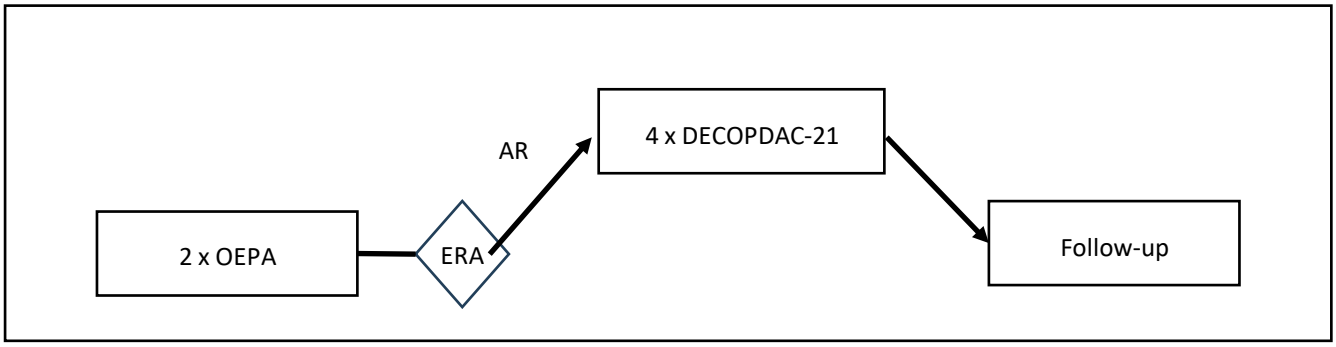


ERA-Inadequate Responders

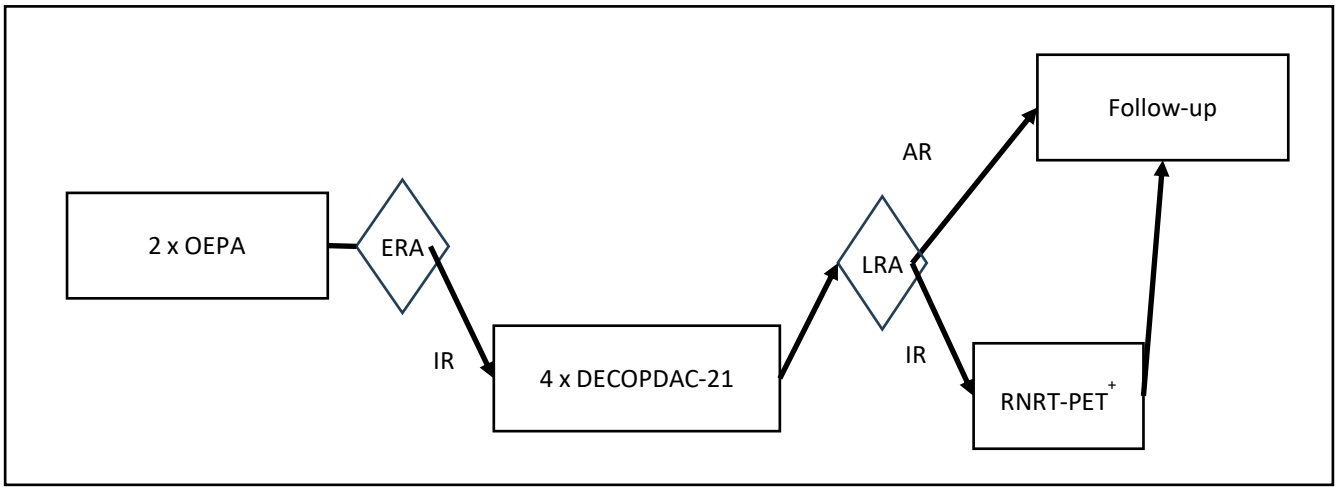


Recommendation for TL-3:

ERA-Adequate Responders



ERA-Inadequate Responders



3.1.2. Treatment plans OEPA, COPDAC-28 and DECOPDAC-21

The first cycle of OEPA starts immediately after completion of staging.
Chemotherapy administration guidelines for all cycles:

- Physical examination
- ALAT, ASAT, GGT, bilirubin, creatinine
- Pregnancy test before start of **each cycle** for female patients of childbearing potential
- Blood counts including differential blood count (**preferably on day 0, 8, 11, 17 and 21 of each cycle of chemotherapy**). *NB: These values had been documented to describe the haematotoxicity profile and to investigate the prognostic value of WBC and neutrophil nadir. The assessments help to guide haematotoxicity in an individual patient but are no longer mandatory outside a trial.*
- ECG, echocardiography
- Pulmonary function test is carried out on investigators' discretion
- Calculation of body surface area takes place before starting each new chemotherapy cycle. Doses should be re-calculated for each cycle on the basis of the most recent BSA.

Chemotherapy continues on **d29** (OEPA, COPDAC-28) or **d22** (DECOPDAC-21) if the following criteria are fulfilled:

- No on-going infections
- WBC > 2,000/mm^3
- ANC > 500/mm^3
- Platelets > 80,000/mm^3

If treatment delay of more than one week is expected, your national chairperson or the ERN PaedCan HL centre in Gießen may be contacted. Expected adverse reactions of the drugs used in OEPA, COPDAC-28 or DECOPDAC-21 are listed below. Chemotherapy cycles should only be interrupted in case of severe infections or other severe complications. Treatment should not be interrupted for cytopenia during the cycle.

Patients may receive hydration with 2.5-3 l/m^2 per day of glucose-saline or normal saline solution concomitantly to chemotherapy for the first cycle of OEPA to prevent tumour lysis syndrome.

If the patient vomits a dose of prednisone/prednisolone within 20 minutes of taking the tablets (or soluble tablets), or if the tablets can actually be seen and counted when the patient vomits more than 20 minutes after administration, the dose should be repeated. If a patient misses a dose normally taken in the morning, s/he may take the dose any time during the same day. However, the missed dose should not be taken on a subsequent day.

OEPA

The first OEPA cycle starts after diagnosis and informed consent is obtained. The OEPA regimen is shown in Tab. 2. Between day 16 and 28 no treatment is administered, the consecutive cycle starts on day 29.

Table 2: OEPA Scheme

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Prednisone/Prednisolone 60 mg/m^2/day p.o. divided into 3 doses day 1 – 15	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Vincristine 1.5 mg/m^2 i.v., capping dose 2 mg day 1 + 8 + 15	●							●							●
Doxorubicin 40 mg/m^2 per 1- 6 hour infusion day 1 + 15	●														●
Etoposide/Etopophos 125 mg/m² Etoposide (**NB:** 142 mg Etoposide phosphate equals 125 mg etoposide); 2hrs infusion time day 1 – 5	●	●	●	●	●										

COPDAC-28 (28-day cycle)

The first COPDAC-28 cycle start as soon as the ERA PET scan is done, ideally on the day of the ERA PET. The COPDAC-28 regimen is shown in Table 3. Between day 16 and 28 no treatment is administered, the consecutive COPDAC-28 cycle starts on day 29 (if applicable).

In line with the drug description, the uroprotectant mesna may be given to minimize urinary tract toxicity, but is not mandatory. If used, an IV bolus of 150 mg/m^2, given at the same time as the cyclophosphamide infusion, should be followed by an IV infusion of 500mg/m^2 over 24 hours on Days 1 and 8. IV hydration is not mandatory, but should be given if the equivalent fluid volume (see Table 3) cannot be given orally.

Dacarbazine is highly emetogenic. Prophylactic antiemetics should be administered according to local policy. Nausea and vomiting should be treated according to established local practice.

Table 3: COPDAC-28 Scheme

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Prednisone/Prednisolone 40 mg/m^2/day p.o. divided into 3 doses (capping dose 80 mg/day) day 1 – 15	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Dacarbazine 250 mg/m^2 per 15 – 30 min. infusion day 1 – 3	●	●	●												

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Vincristine 1.5 mg/m^2 i.v. capping dose 2 mg day 1 + 8	●							●							
Cyclophosphamide 500 mg/m^2, per 60 min. infusion day 1 + 8 optional concomitant intravenous hydration with glucose/saline solution at a rate of 3 l/m^2 over 24 hours	●							●							

DECOPDAC-21 (21-day cycle)

The first DECOPDAC-21 cycle starts as soon as the ERA PET is done, ideally on the day of the ERA PET. The DECOPDAC-21 regimen is shown in Tab. 4. Between day 9 and 21 no treatment is administered, the consecutive cycle starts on **day 22.**

Dacarbazine is highly emetogenic. Prophylactic antiemetics should be administered according to local policy. Nausea and vomiting should be treated according to established local practice.

In line with the drug description, the uroprotectant mesna may be given to minimize urinary tract toxicity but is not mandatory. An IV bolus of 300 mg/m2, given at the same time as the cyclophosphamide infusion, should be followed by an IV infusion of 625 mg/m2 over 24 hours on Days 1 and 2. IV hydration is not mandatory, but should be given if the equivalent fluid volume (see Table 5) cannot be given orally.

Prophylactic use of G-CSF is not recommended. G-CSF 5 µg/Kg BW may be given subcutaneously from day 9 to day 15 in individual patients if severe infection or significant treatment delay have occurred.

Once the anthracycline dose increases over 200mg/m^2 in the DECOPDAC-21 arm please perform an echocardiography before the start of DECOPDAC-21 cycle 5 and cycle 6. If cardiac function is impaired (either the shortening fraction is less than 29% or there is a greater than 10% reduction in the shortening fraction compared to the last echo) please contact the national chairperson or the ERN PaedCan HL centre in Gießen for advice.

Table 4: DECOPDAC-21 Scheme

Day	1	2	3	4	5	6	7	8
Prednisone/Prednisolone 40 mg/m^2/day p.o. divided into 3 doses, day 1 – 8, no capping dose prescribed	●	●	●	●	●	●	●	●
Dacarbazine 250 mg/m^2 per 15 – 30 min. infusion day 1 – 3	●	●	●					
Vincristine 1.5 mg/m^2 i.v. capping dose 2 mg day 1 + 8	●							●
Cyclophosphamide 625 mg/m^2, 60-min. infusion day 1 and day 2	●	●						

Day	1	2	3	4	5	6	7	8
optional: concomitant intravenous hydration with glucose/saline solution at a rate of 3 l/m^2 over 24 hours								
Etoposide/Etopophos 100 mg/m^2/day Etoposide infusion over 2 hrs **NB:** 113.6mg Etoposide phosphate equals 100 mg Etoposide) day 1 – 3	●	●	●					
Doxorubicin 25 mg/m^2 per 1- 6 hour infusion day 1	●							

3.1.3. Radiotherapy

For patients in all treatment levels (TL-1, TL-2 and TL-3), the decision on radiotherapy is based on early response assessment after 2 cycles of OEPA. Patients with adequate response (AR) will not receive radiotherapy.

A short overview of important definitions is provided within this treatment guideline:

Target Volumes

For details on target volume definitions like gross tumour volume (GTV), clinical tumour volume (CTV) and planning target volume (PTV) please refer to your radiooncology centre or the Radiotherapy Manual version 5.0 of the previous EuroNet-PHL-C2 trial.

Principles of radiotherapy application are described below.

The term modified involved field radiotherapy (mIFRT) was used to describe the RT field volume in EuroNet-PHL-C1, the GPOH-HD-2002 GPOH-HD-95 and DAL-HD-90 trial. In this study the term “involved node radiotherapy” (INRT) will replace the expression “modified involved field radiotherapy“ (mIFRT), since 3D target definition will be based on involved lymph nodes. The resulting volume is not expected to differ significantly from the previously defined modified involved field technique.

ERA PET-positive patients in TL-1 or in TL-2 and TL-3 in the COPDAC-28 arm

The target volume definition in patients in TL-1 and in patients in TL-2 and TL-3 treated in the COPDAC-28 arm will be based on initial nodal and extra-nodal involvement, as presented on the staging PET-CT scans at the time of diagnosis.

In TL-2 and TL-3 patients late response assessment (LRA-PET) will be performed after end of chemotherapy to determine the need for boost. If residual lymph nodes > 1 cm are still PET-positive at LRA-PET, 10 Gy boost will be administered to any of these lesions.

Note: Initially involved organs will only require radiotherapy if they are still positive at ERA-PET assessment. E-lesion, i.e. contiguous infiltration of a lymph node mass into extra-lymphatic structures or organs will receive radiotherapy irrespective of ERA-or LRA PET results, since it would be senseless to irradiate all initially involved lymph node, but not the lymph node extensions into an organ or other extra-lymphatic tissue. Total lung, pericardial and liver irradiation will be avoided wherever possible.

ERA PET-positive patients in TL-2 and TL-3 in the DECOPDAC-21 arm

The target volume definition for patients in TL-2 and TL-3 in the DECOPDAC-21 arm will be restricted only to any LRA PET-positive lymph node > 1cm at the end of all chemotherapy. If more than one lesion is LRA PET-positive they should be delineated as **one** target wherever feasible to avoid multiple small fields (patchwork irradiation).

E-lesions and organ involvement will only require radiotherapy if these lesions are LRA PET-positive at the end of chemotherapy. Total lung, pericardial and liver irradiation will be avoided wherever possible.

Timing of Radiotherapy

In patients with inadequate response at ERA radiotherapy should start as soon as possible after decision on the radiotherapy indication within the local MDT. In TL-1 patients ERA-PET and in TL-2 and TL-3 patients LRA-PET **is time critical** for RT planning. Radiotherapy should start ideally within two weeks after response assessment. Delays of more than four weeks **must** be avoided**.**

In case of both supra- and infra-diaphragmatic tumour involvement, radiotherapy may be performed sequentially depending on the radiation volume (small supra- and infra-diaphragmatic volumes can be irradiated at the same time). If the volumes are treated separately, the gap between the first and second series should not be longer than one week.

Organs at Risk (OAR)

Radiosensitivity of normal tissues varies with age. Radiation effects are more significant in young children than in older children or adults. Soft tissue, bones, thyroid gland, lung, spinal cord, heart, large vessels, breasts, kidney, liver and gonads are regarded as organs at risk. Relevant organs at risk must be delineated on the treatment planning scan.

Bony structures within and adjacent to the PTV should be delineated in young children. **Dose constraints** for whole kidneys (12 Gy), whole lung (15 Gy), whole liver (15 Gy), testis (< 1 Gy) and ovary (< 5 Gy) must be taken into account and the dose to normal structures should be kept as low as reasonably achievable.

Radiotherapy Planning and Radiotherapy Doses

Details of the organisation of radiotherapy planning as well as the recommended radiotherapy techniques should be discussed with your radiooncology centre and or you should refer to the Radiotherapy Manual version 5.0 of the previous EuroNet-PHL-C2 trial.

Radiotherapy should be given daily (five days per week). Treatment interruptions must be kept to a minimum.

For patients in TL-1 and in TL-2 and TL-3 in the **COPDAC-28** arm, the standard radiotherapy dose consists of **19.8 Gy in 11 fractions** (1.8 Gy per fraction). If required in TL-2 and TL-3 patients, the boost dose is 10 Gy in 5 fractions (2 Gy per fraction) for LRA PET positive residuals. In all patients in the **COPDAC-28** arm, E-lesions should be treated to **19.8 Gy in 11 fractions**, or the appropriate tolerance dose to the OAR.

For patients in TL-2 and TL-3 in the **DECOPDAC-21** arm with positive LRA-PET, the prescribed dose is **28.8 Gy in 16 fractions** (1.8 Gy per fraction). In patients in the **DECOPDAC-21** arm positive E-lesions at LRA-PET require **28.8 Gy in 16 fractions** (1.8 Gy per fraction) or the appropriate tolerance dose to the OAR. For exception see the Radiotherapy Manual version 5.0 of the previous EuroNet-PHL-C2 trial.

If whole lung irradiation (unilateral and bilateral) is prescribed, the dose should not exceed 12 Gy if both lungs are involved and 14.4 Gy for unilateral involvement. The fraction size should not exceed 1.2 Gy.

Technical Requirements

Radiotherapy should be delivered with high energy photons. Alternatively, in **selected cases** radiotherapy can be delivered with protons if this is accepted standard of care by the relevant national

regulatory authorities. The choice of the treatment technique is left to the discretion of the treating radiation oncologist.

The following equipment is required:

- Computed tomography for treatment planning
- 3D Treatment Planning System integrating 3D sectional imaging, DVH
- Linear accelerators with photon energies of 4 - 6 (- 10) MV or cyclotron or synchrotron for radiotherapy with protons
- Multileaf collimators and/or conformal blocks for individual shielding, in case of proton radiotherapy passive scattering or scanning beams delivery with aperatures and/or compensators, as appropriate, to shape the fields laterally and distally
- LINAC on-board verification system (EPIDs, CBCT, ExacTrac system) or equivalent verification system for use of proton radiotherapy
- LINAC on-board verification system (EPIDs, CBCT, ExacTrac system) or equivalent verification system for use of proton radiotherapy

Adverse Reactions of Radiotherapy

Adverse reactions

Adverse reactions like nausea, mucositis, erythema, hair loss, dry mouth, diarrhoea, leucocytopenia, and thrombocyctopenia occurring during radiotherapy with less than 19.8 Gy are rare and mostly temporary. The nature and severity of adverse reactions will also depend on the site irradiated, field size, and the chemotherapy received. Most acute side effects can be treated symptomatically and are self-limiting.

Late 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 young adults, but most children with Hodgkin lymphoma are over age 6. Late effects reflect the location and field size and dose of radiotherapy as well as the type of chemotherapy received, e.g. doxorubicin. Radiation-induced changes in organs and tissues may develop after long latency periods and may not become clinically evident until puberty or adulthood. Secondary malignancies (e.g. increased risk of breast and thyroid cancer) may increase after 20 to 30 years, and these, together with cardiac late effects, remain a major cause of mortality in long-term survivors.

The documentation of long-term side effects is strongly recommended within the relevant different national databases.

Ovariopexy

Whenever iliac nodal sites have 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 potentially leading to significant long-term ovarian impairment. This can usually be avoided when using opposed fields with 19.8 Gy, and if the ovary is more than 2 cm distant from the adjacent field (shield) border.

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

Radiotherapy Quality Assessment

Quality control (QC) is an essential component of radiotherapy planning and treatment. Therefore, we recommend that data from all patients receiving radiotherapy will be reviewed and analysed by reference radiooncology teams, where available. Outside a dedicated trial protocol, QC may me more difficult to obtain, but my often be requested in national pediatric radio-oncology centres.

3.2. Assessments

Response Assessment

3.2.1. Early Response Assessment

The ERA PET scan (Im-2) is performed 14-17 days (i.e. day 29 – 32 of the second OEPA) after the last dose of prednisone/prednisolone in OEPA cycle 2. Note: Prednisone/prednisolone must not be tapered (Stop on day 15 of OEPA).

For all sites with visibly enhanced FDG-uptake the visual Deauville score will be determined and documented. (The qPET-value may be determined at the ERNPaedCan centre in Gießen, only upon special request).

The decision on radiotherapy indication at ERA will be based on the Deauville score aided by the qPET-value (note: the qPET value was decisive within the EuroNet-PHL-C2 trial).

The response is **ERA PET-positive** if at least one site corresponds to Deauville 4+ which is equivalent to a is **qPET-value ≥ 1.3**. Otherwise the response will be **ERA qPET-negative**.

In contrast to EuroNet-PHL-C1, the morphological response is assessed in the initially largest reference volume only. Bulk is present if the largest reference volume exceeds 200 ml. **Poor Bulk Response** is defined as volume reduction of less than 50% of the initial volume.

If no tumour progression is detected, response groups are defined based on Deauville score aided by the qPET-value and by bulk response.

Inadequate response (IR):

- ERA PET at Deauville ≥ 4 which is equivalent to qPET ≥ 1.3 **and/or**
- Poor bulk response (< 50% volume reduction) **and/or**
- At least one nodal site with largest diameter of ≥ 2 cm and non-assessable qPET-value due to brown fatty tissue.

Adequate response (AR):

- No IR criterion fulfilled

Patients with AR do not receive radiotherapy.

3.2.2. Late Response Assessment

PET at LRA (Im 3) will be performed 14 – 17 days after the last dose of prednisone/prednisolone in the second (TL-2) or fourth (TL-3) COPDAC-28 (i.e. LRA at day 29 - 32 of the last COPDAC-28) or DECOPDAC-21 cycle (i.e. LRA at day 22 – 25 of the last DECOPDAC-21). Prednisone/prednisolone must not be tapered. Important time lines for continuation of treatment are described in detail in **Appendix VI.**

For late response assessment only sites with morphologic residuals ≥ 1 cm are considered. A site is **LRA PET-positive** if the **Deauville 4+ which is equivalent to *qPET value is* ≥ *1.3.***

All LRA qPET-positive sites must be identified.

Patients in TL-2 or TL-3 in the COPDAC-28 arm receive 10Gy boost irradiation to LRA qPET-positive sites (Radiotherapy field is based on pre-treatment sites.).

Patients in TL-2 or TL-3 randomised to DECOPDAC-21 receive radiotherapy to LRA qPET-positive sites only (Radiotherapy field is restricted to LRA PET positive residua only.).

3.2.3. Progression or Relapse Definitions

Progression or relapse is **suspected** if

- at least one initially involved mass increases by more than 25% compared to the best previous response or
- new lymphatic or extra-lymphatic lesions occur
- B-symptoms (re)occur which cannot be explained otherwise.

Biopsy of enlarging or new lesions is mandatory to confirm progression or relapse.

Reference pathology including subtyping and immunochemistry should be obtained as soon as possible after salvage treatment start (for details see **Appendix IV.3**).

The date of the biopsy defines the time point of disease recurrence. Disease recurrence is defined as

- **Primary Progression,** if it occurs on or within three months after end of treatment
- **Early Relapse,** if it occurs > 3 to 12 months after end of treatment
- **Late Relapse,** if it occurs > 12 months after end of treatment

3.3. Summary of known adverse events associated with treatment recommendation

Adverse Reactions of Chemotherapy

Common adverse reactions of chemotherapy are nausea, vomiting, weight loss and alopecia. Late effects of chemotherapy may be risk of secondary malignancies, infertility, premature menopause or cardiovascular damage.

Etoposide

Common adverse reactions of Etoposide are allergic reactions, mucositis, peripheral neuropathy, CNS toxicity, myelotoxicity.

Dacarbazine (DTIC)

Dacarbazine is highly emetogenic. Diarrhoea, influenza-like symptoms, allergic skin reactions, fever, photosensitization, local vein irritation as well as flush symptoms may occur during or after drug infusion. Myelotoxicity is generally low. Rarely liver, kidney and CNS toxicities (apathy, seizures) occur. A mutagenic, carcinogenic and teratogenic effect of DTIC has been demonstrated in animal studies. During the GPOH-HD 2002 trial one patient died of rhabdomyolysis after DTIC.

Vincristine (VCR)

Common adverse reactions 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 limbs replacement of vincristine by vinblastine at a dose of 6 mg/m^2 (capping dose 10 mg) is recommended.

Cyclophosphamide

Common adverse reactions of cyclophosphamide are myelotoxicity, increased risk for infections, haemorrhagic cystitis. The risk for haemorrhagic cystitis following cyclophosphamide is dose-dependent. For recommendations on the use of mesna for uroprotection please see Sections 12.6.2 and 12.6.3.

Doxorubicin

Adriamycin (doxorubicin) even at low cumulative doses can lead to permanent myocardial damage. However, the extent of long-term cardiac risks is unknown. Therefore, before start of treatment the cardiac function has to be examined by echocardiography and documented. In case of initial damage of the heart function a therapeutic alternative should be discussed with the trial centre in Gießen.

Prednisone/prednisolone

Prednisone/prednisolone treatment is associated with a risk of osteonecrosis (avascular necrosis) which is well described in patients being treated for acute leukaemia. In rare cases joint replacement may be required. In addition, the prednisone/prednisolone therapy may lead to reversible retention of water, weight gain, increased risk of infection and psychosis/mental disorders. The prednisone/prednisolone dose in COPDAC-28 is capped at 80mg per day.

3.4. Dose Modifications and delays

Dose and Treatment Modifications

Dose management in obese patients (body mass index>30kg/m2)

Doses of IMPs will not be capped in obese patients, or others whose BMI is outside the normal range, other than where specified (Section 12.6.2, Table 4, prednisone dose in COPDAC-28), in line with the recommendations in the Clinical Practice Guideline published by the American Society of Clinical Oncology (Griggs et al., 2012).

Other dose modifications

Since the chemotherapy regimens are generally well tolerated no provisions for dose modifications are given. Haematotoxicity of CTC grade 4 is a common finding during the OEPA regimen. Treatment delays should be avoided, any deviation from the protocol specification has to be documented in the patient files and on the respective CRF-pages. In case of drug-specific toxicity (examples: doxorubicin-related impaired cardiac function, severe neuropathy during or after vincristine) or other unexpected severe adverse events must be reported on the respective SAE reporting/toxicity forms. The following modifications in case of complications are recommended:

Vincristine

- **Seizures:** Hold 1 dose, then reinstitute.
- **Severe foot drop, paresis or ileus:** Hold dose(s); institute aggressive regimen to treat constipation (except enemas if neutropenic), if present. When symptoms abate, resume at 1mg/m²; escalate to full dose as tolerated.
- **Jaw pain:** Treat with analgesics; do not modify vincristine dose.
- **Hyperbilirubinemia: Check LFTs only if patient jaundiced.**
- Withhold if total bilirubin > 50 **µmol/L**. Administer 50% of dose if total bilirubin 25 - 50 **µmol/L**.
- **Do not alter dose for abnormal transaminases.**

Steroids

- **Hypertension:** Steroid should not be reduced. Sodium restriction and anti-hypertensives may be employed in an effort to control hypertension.

- **Malignant Hypertension:** Reduce dose by 33%. Sodium restriction and antihypertensive drugs may also be utilized.
- **Hyperglycemia:** Steroids should not be reduced if the patient develops clinical signs of diabetes. Rather, insulin therapy should be employed to control the blood glucose level such that symptoms and signs are minimal.
- **Pancreatitis:** Do not modify dose.
- **Psychosis:** Administer half dosage of steroid.
- **Suspected steroid-induced myopathy:** Measure CPK with isoenzymes, consider EMG studies.
- **Avascular necrosis:** Contact national chairperson or trial office in Gießen if AVN occurs.
- **Varicella Zoster:** Discuss with trial office in Gießen or the national chairperson in case of active infection. They should not be withheld during incubation period following exposure to varicella.
- In some patients prednisolone has led to severe allergic reactions with circulation problems, cardiac arrest, arrhythmia, bronchospasm, increased or decreased blood pressure

Doxorubicin

- **Hyperbilirubinemia**
    - If total bilirubin >120 µmol/L omit dose
    - If > 90 µmol/L but ≤ 120 µmol/L give 25% of dose
    - If > 50 µmol/L but ≤ 90 µmol/L give 50% of dose
    - If ≤ 50 µmol/L give full dose
    - Check LFTs only if patient is jaundiced. Do not alter dose for abnormal transaminases.
- **Dose adaptation due to cardiotoxicity**
    - If temporary deterioration of myocardial function occurs, e.g. decrease in fractional shortening to < 29%, or a decrease of 10% or more relative to previous tests, and if this is confirmed by a repeat echocardiogram, omit doxorubicin in the next course and discuss alternatives with the trial office in Gießen or the national chairperson.
    - If persistent deterioration of myocardial function occurs, e.g. persistent decrease in fractional shortening by an absolute value of 10 percentile points from previous tests or a persistent fractional shortening < 29%, 40% LVEF, avoid further doxorubicin and discuss alternatives with the trial office in Gießen or the national chairperson.

Cyclophosphamide

- **Gross haematuria**: Hydrate at 125 ml/m²/hr for 24 hours after dose and use mesna infused alongside hydration fluid according to local established practice.
- **Acute fluid retention**: Treat with furosemide.

In case of other complications, the trial office in Gießen should be consulted to discuss therapeutic alternatives.

3.5. Supportive Treatment

Supportive Treatment

Antibacterial prophylaxis

All patients should receive **co-trimoxazole (trimethoprim/sulphamethoxazole)** for PCP prophylaxis during chemo- and radiotherapy and up to three months after end of chemo-radiotherapy or according to local standard practice. **PCP prophylaxis is mandatory.**

Antifungal prophylaxis

During chemotherapy and radiotherapy patients may receive antifungal prophylaxis according to local practice. This is not mandatory. Oral anti-fungals in the 'azole' group (flu-, itra-, vori- conazole should not be administered within 48 hours before or after Vincristine due to drug interactions).

Prevention of GvH reaction/infection through blood transfusions

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

Supportive care

Generally, PICC/Portacath/Hickman line insertion prior to treatment is recommended to avoid extravasation particularly of doxorubicin. In the presence of large mediastinal mass and/or venous compression delay in placement of the central line until the second cycle of chemotherapy may reduce the risk of CVC related thrombosis.

3.6. Patient Follow Up

Follow-up Recommendations

Diagnostics	1 year	2. + 3. Year	4. + 5. year
Complete clinical examination and follow-up	6 weeks and 3, 6, 9 and 12 months after end of treatment	Every four months	Every six months
Chest X-ray	6 months and 9 months after end of treatment	Every four months	
Ultrasound neck, abdomen and pelvis	6 and 9 months after end of treatment	Every four months	Every six months
Chest CT in patients with initial lung involvement	3 months and 12 months after end of treatment*		
MRI of all initially involved regions	3 months and 12 months after end of treatment* No i.v.		

	contrast agent necessary		
Lung function testing; Echocardiography	3 months	Once every two years	Once every two years
T4, TSH, ultrasound of thyroid	Once a year	Once a year	Once a year

Note: Routine FDG-PET for follow-up is not recommended.

Additional cross-sectional imaging in the event of suspected relapse would be carried out according to routine local practice.

Some countries may consider it appropriate to perform fewer investigations as part of their follow-up procedures.

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APPENDIX 1 - TUMOUR STAGING

Please refer to chp. 2.1. Lymphoma assessment, Staging Criteria and Treatment Level Allocation of the present Treatment Guideline.

APPENDIX 2 – SCREENING PROCEDURES

The following assessments and procedures must be performed prior to start of treatment.

2.1. Histopathology

- **Biopsy and confirmation of diagnosis:** The histo-pathological diagnosis is based on biopsy of lymph nodes or other primarily involved organs before trial entry. Biopsies should be excision or tru-cut biopsies where adequate diagnostic material is obtained. Fine needle aspiration biopsies are not appropriate.
- **Pathology Review is preferred** for all patients being treated according to this guideline.

  Pathology Review is carried out at initial diagnosis and relapse diagnosis.

  The local Investigator is responsible for ensuring that the correct materials (tissue and documentation) are submitted for to the appropriate Reference Pathologist immediately after treatment start.

- ***Note - in the event of relapse that - Relapse is diagnosed by biopsy*** *of lymph nodes or other primarily involved organs. The local Investigator is responsible for ensuring that the correct materials are submitted to the appropriate Reference Pathologist as soon as a local relapse diagnosis has been made.*

2.2. Full medical history and physical examination:

- Height, weight and body surface area
- Assessment of clinical symptoms including B-symptoms
- History of clinical symptoms
- Assessment of paraneoplastic phenomena
- History of prior treatment

2.3. Further assessments and tests

2.3.1. Mandatory

- **Erythrocyte Sedimentation Rate** (ESR; I hour) – **essential** for Treatment Level allocation
- CRP (for correlation with ESR)
- Serum albumin
- Complete blood count (Hb, WBC, platelets, lymphocytes, neutrophils)
- TSH and fT4
- Liver function tests (ALAT (GPT), ASAT(GOT), GGT, bilirubin)
- Creatinine and sodium, potassium, calcium, phosphorous
- Coagulation screen (INR, PTT)
- ECG and Echocardiogram
- HIV serology
- Pregnancy test for all female patients of child bearing age. Carried out no more than 2 weeks before starting treatment.
- Fertility considerations: Semen cryopreservation before treatment should be offered to post-pubertal male patients. At centres with IRB/ethical approvals ovarian cortical tissue harvesting (or egg cryopreservation after hormone stimulation in post menarchal females) may be offered to patients who are likely to receive pelvis radiation.

2.3.2. Recommended

- Fibrinogen
- Ferritin
- LDH, AP

- Protein electrophoresis (gamma-globulin and alpha-2 globulin)
- Immunoglobulin A, G and M

Baseline virology including serology examinations for antibodies against VZV, EBV, CMV, HSV, toxoplasmosis, hepatitis A, B, C (HCV-PCR).

2.4. Imaging Options

2.4.1: Staging

There are three options - within the selected option all of the imaging is mandatory.

Option A)

- **Whole-body PET-MRI with i.v. contrast** (acquisition from skull base to mid thighs and respiratory triggering for chest and abdomen)
- Chest CT (to detect lung involvement) of diagnostic quality in end-inspiration
- Abdominal ultrasound (to detect liver and spleen involvement)
- **IF** skeletal involvement is detected (without CT correlation) then a whole body bone scan is also required

Option B)

- **Whole-body PET-CT (low dose) with i.v. contrast** (acquisition from skull base to mid thighs and respiratory triggering for chest and abdomen)
- Chest CT (to detect lung involvement) of diagnostic quality in end-inspiration.
- Abdominal ultrasound (to detect liver and spleen involvement)

Option C)

- **Whole body PET-CT (low dose) without i.v. contrast (not recommended!) or PET only** (acquisition of from skull base to mid thighs)
- Chest CT (to detect lung involvement) of diagnostic quality in end-inspiration.
- MRI (or diagnostic quality CT) with i.v. contrast of neck, abdomen and pelvis
- Abdominal ultrasound (to detect liver and spleen involvement)
- **IF** skeletal involvement is detected (without CT correlation) then a whole body bone scan is also required

Recommended options are A and B

2.4.2: Early Response assessment (ERA)

Techniques are based on the option used at staging and initial areas of disease

Option A)

- **Whole-body PET-MRI with i.v. contrast** (acquisition from skull base to mid thighs and respiratory triggering for chest and abdomen) – and -

- IF initial lung involvement - Chest CT of diagnostic quality in end-inspiration

Option B)

- **Whole-body PET-CT (low dose) with i.v. contrast** (acquisition from skull base to mid thighs and respiratory triggering for chest and abdomen) – and -
  - IF initial lung involvement - Chest CT of diagnostic quality in end-inspiration

Option C)

- **Whole body PET-CT (low dose) without i.v. contrast (not recommended!) or PET only** (acquisition of from skull base to mid thighs)
- MRI (or diagnostic quality CT) with i.v. contrast of neck, abdomen and pelvis – and -
  - IF initial lung involvement - Chest CT of diagnostic quality in end-inspiration

2.4.3: Late Response Assessment (LRA) - For TL-2 and TL-3 Patients who are ERA PET Positive:

Techniques are based on option used at staging and initial areas of disease

Option A)

- **Whole-body PET-MRI with i.v. contrast** (acquisition from skull base to mid thighs and respiratory triggering for chest and abdomen) – and -
  - IF initial lung involvement - Chest CT of diagnostic quality in end-inspiration

Option B)

- **Whole-body PET-CT (low dose) with i.v. contrast** (acquisition from skull base to mid thighs and respiratory triggering for chest and abdomen) – and -
  - IF initial lung involvement - Chest CT of diagnostic quality in end-inspiration

Option C)

- **Whole body PET-CT (low dose) without i.v. contrast (not recommended) or PET only** (acquisition of from skull base to mid thighs)
- MRI (or diagnostic quality CT) with i.v. contrast of neck abdomen and pelvis – and -
  - IF initial lung involvement - Chest CT of diagnostic quality in end-inspiration

2.4.4: Late Response Assessment (LRA) - For TL-2 and TL-3 Patients who are ERA PET Negative

- **LRA PET scan is NOT required**

End of treatment conventional cross-sectional imaging is carried out according to local standard practice – in order to ensure that there is no disease progression during consolidation chemotherapy.