EUROPEAN STANDARD CLINICAL PRACTICE RECOMMENDATIONS

FOR NON-HODGKIN LYMPHOMA OF CHILDHOOD AND ADOLESCENCE

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Recommendations are based on:

NHL-BFM 95 and EICNHL EURO LB 2002 TRIALS
NHL-BFM REGISTRY
INTERNATIONAL RITUXIMAB TRIAL for HIGH-RISK MATURE B-NHL (EICNHL, COG)
EICNHL ALCL99 TRIAL

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LIST OF ABBREVIATIONS

ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukemia
Ara-C	cytarabine
B-AL	Burkitt leukemia
BL	Burkitt lymphoma
BM	bone marrow
BMP	bone marrow puncture
BSA	body surface area
CCG	Children's Cancer Group
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CT	Computerized tomography
DLBCL	diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
ECG	electrocardiogram
EFS	event-free survival
EICNHL	European Intergroup for Childhood Non-Hodgkin Lymphoma
FAB	French-American-British
FISH	fluorescence in situ hybridization
gamma GT	gamma-glutamyl transferase
GvHD	graft versus host disease
Gy	Gray
HD	high-dose
HIV	human immunodeficiency virus
HR	high risk
i-BFM	international Berlin-Frankfurt-Münster
IPNHLSS	International Pediatric Non-Hodgkin Lymphoma Staging System
IT	intrathecal
IV	intravenous
LBCL	large B-cell lymphoma
LBL	lymphoblastic lymphoma
LCV	folinic acid (leucovorin)
LDH	lactate dehydrogenase
LMB	Lymphome Malins de Burkitt
LP	lumbar puncture
LVF	left ventricular function
MDD	minimal disseminated disease

MRD	minimal residual disease
MRI	magnetic resonance imaging
MTX	Methotrexate
NHL	non-Hodgkin lymphoma
NPM	Nucleophosmin
OS	overall survival
pB	precursor B-cell
PEG	pegylated
PET-CT	positron emission tomography–computed tomography
PMLBCL	primary mediastinal large B-cell lymphoma
SFOP	French Society of Paediatric Oncology
SGOT	serum glutamic-oxaloacetic-transaminase
SGPT	serum glutamic-pyruvic-transaminase
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SR	standard risk
TLS	tumor lysis syndrome
TMP	Trimethoprim
TPMT	Thiopurinmethyltransferase
UKCCSG	United Kingdom Children's Cancer Study Group (now CCLG)
VBL	Vinblastine
VCR	Vincristine
VDS	Vindesine
VOD	veno-occlusive disease
VZV	varicella zoster virus
WBC	white blood cell count
WHO	World Health Organization

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1. BACKGROUND AND RATIONALE

Non-Hodgkin Lymphoma (NHL) is the fourth most common subtype of malignancy diagnosed in children and adolescents. The most prevalent histological subtypes of NHL of childhood and adolescence are Burkitt Lymphoma (BL), T- and B-cell (pB) Lymphoblastic Lymphoma (LBL), Anaplastic Large Cell Lymphoma (ALCL) and Diffuse Large B-Cell Lymphoma (DLBCL) accounting for 48%, 21%, 10% and 8% of all pediatric NHL, respectively.[1]

The following paragraphs summarize treatment strategies for the 3 main subtypes of NHL in childhood and adolescence (LBL, mature aggressive B-cell NHL and ALCL) including relevant results of previous trials conducted by international study groups.

1.1 Lymphoblastic Lymphoma

Lymphoblastic lymphoma in children and adolescents develops from T-cell (75%) and precursor B-cell lymphocytes (25%).[1] Both LBL subtypes are treated according to the same treatment strategy.

The following table summarizes treatment results from trials in pediatric patients with LBL.

Table 1.Treatment results from trials in pediatric patients with LBL

Trial	Age	Stage	Treatment	No. pts	pEFS	Reference
LMT81	9y (0.9-16)	I-IV	mod. LSA2-L2	84	75±3%	Patte et al. 1992[2]
CCG502	9y (0.5-19)	I-IV	mod. LSA2-L2 vs ADCOMP	143 138	74% 64%	Tubergen et al. 1995[3]
POG8704	10y (5-15)	III/IV	L-Asp - vs L-Asp +	83 84	64±6% 78±5%	Amylon et al. 1999[4]
NHL-BFM90	9y (1-16)	I-IV	ALL-BFM	105	90%	Reiter et al. 2000[5]
NHL-BFM95	8y (0.2-19)	III/IV	ALL-BFM	169	78±3%	Burkhardt et al. 2006[6]
EORTC58881	8y (0-16)	I-IV	ALL-BFM	119	78±3%	Uyttebroeck et al. 2008[7]
COG Pilot	n.d.	III/IV	mod. LSA2-L2	85	78±5%	Abromowitch et al. 2008[8]
COG A5971	10y	III/IV	NHL-BFM95 MTX w/o HDMTX intensification w/o intensification	total 257	85±4% 83±4% 83±4% 83±4%	Abromowitch et al. 2008 [Abstract ASH 2008][9]
LNH92	8y (0-<16)	I-IV	mod. LSA2-L2	55	69±6%	Pillon et al. 2009[10]
St. Jude 13	n.d.	III//V	T-ALL	41	83%	Sandlund et al. 2009[11]
POG 9404	50% <10y	III//V	mod. DFCI ALL with HDMTX w/o HDMTX	137 66 71	82 ±5% 88 ±4%	Asselin et al. 2011[12]
A 5971	>12mo	I-II	CCG-BFM	56	90%	Termuhlen et al. 2012[13]
EURO-LB 02	0-<21y	I-IV	NHL/ALL-BFM 90 Dexa (10mg/m2) vs Pred (60mg/m2)	319 98 88	82±2% 84±4% 84±4%	Landmann et al. 2017[14]
EORTC58951	n.d.		mod. BFM 90 Dexa (6mg/m2) vs Pred (60mg/m2)	37 37	85% 89±5% 81±6%	Uyttebroeck et al. 2012[15] (Abstract)
SFOP LMT96	10.5y		mod. BFM	79	85%	Bergeron et al. 2015[16]

Lymphoblastic lymphoma shares common morphological, immunophenotypic and clinical characteristics with acute lymphoblastic leukemia (ALL). Thus, the therapeutic approach in Europe is

mainly based on a backbone of ALL protocols (derived from the Berlin-Frankfurt-Münster (BFM) Study Group), consisting of a 9-week induction, an 8-week consolidation and a 7-week re-induction treatment followed by an oral maintenance to a total therapy duration of 2 years.[5,17,18]

Although the prognosis for relapsed/refractory patients remains dismal, the 5-year event-free survival (EFS) and overall survival (OS) for newly diagnosed pediatric LBL patients has substantially increased throughout the years, with the NHL-BFM 90 trial achieving the best results so far (EFS 90%).[5,19] The subsequent trial, NHL-BFM 95 tested whether prophylactic cranial irradiation can be omitted in CNS-negative patients with advanced stages of disease compared to the historical control. According to the statistical plan of the trial, it was shown that omission of prophylactic cranial irradiation in CNS-negative patients with stage III or IV LBL and sufficient response to induction therapy, may result in a non-inferior survival.[6] However, the EFS of the NHL-BFM 95 trial was inferior to that of the NHL-BFM 90 trial.

For the EURO-LB 02 trial of the European Intergroup for Cooperation on Childhood NHL (EICNHL) it was accepted that the NHL-BFM 90 trial should be the reference arm for the study. The primary objectives of this randomized trial were to test whether replacing prednisone with dexamethasone during the induction phase increases EFS in the subgroups with T-cell LBL and whether the maintenance therapy duration could be reduced from 24 to 18 months total therapy duration. These questions could not be answered because of the primary closure of the study due to an unacceptable high rate of treatment-related deaths. The study achieved an EFS of 82±2%, inferior to the 90% of the NHL-BFM 90 trial, attributable to higher rates of toxic deaths and CNS relapses (only in the prednisone arm). In conclusion, results of the trial suggest that dexamethasone in induction may prevent CNS relapse more effectively than prednisone, but produces a higher burden of toxicity.[14]

In August 2019, the international cooperative randomized LBL-2018 trial opened, recruiting patients younger than 18 years with newly diagnosed LBL. This protocol uses the NHL-BFM 90 backbone, like the preceding EURO-LB 02 trial. The primary aims of the study are to determine whether the cumulative incidence of relapses with involvement of the CNS can be decreased with an induction therapy phase including two weeks of dexamethasone (10 mg/m²/d) instead of 3 weeks of prednisone (60 mg/m²/d), and if EFS in high-risk LBL patients can be improved by intensified consolidation therapy. In addition, molecular stratification of T-LBL patients was introduced for the first time in the LBL-2018 trial. Data from the international co-operation of the Italian study group (AIEOP), the French study group (SFCE) and the German study group (BFM-G) showed that the mutational status of *NOTCH1* and/or *FBXW7* genes defined a favorable risk group with an EFS of about 90%, as compared to the wild-type status (EFS 70%), classifying these patients as standard-risk.

In the AIEOP-BFM ALL 2009 trial and in several studies from other study groups, ALL patients nowadays receive pegylated (PEG) asparaginase instead of native E. coli asparaginase as for first-line therapy, and it has been demonstrated that the use of PEG asparaginase in front-line treatment for childhood and adult ALL is effective, with a tolerable toxicity profile, similar to that observed with the native product.[20-23] Moreover, a decrease in hypersensitivity and silent inactivation has been observed. Therefore native E. coli asparaginase is currently substituted by PEG asparaginase in front-line therapies of LBL.

The LBL-2018 trial completely omits cranial irradiation. Recent studies by international ALL study groups suggest that omission of cranial irradiation is possible in combination with intensified CNS-targeted therapy.[24-27] In addition, the St. Jude NHL13 and EORTC 58881 trials showed that cranial irradiation can be omitted for all LBL patients without comprising EFS and OS.[11,28]

1.2 Mature Aggressive B-Cell Lymphoma/Leukemia

Mature aggressive B-NHL accounts for approximately 60% of NHL among children and adolescents.[1,29] The main subtypes include BL, mature B-cell Acute Leukemia (B-AL) and DLBCL as well as primary mediastinal large B-cell lymphoma (PMLBCL). Combination chemotherapy, refined by incorporation of new active agents succeeded with an overall survival of 90% in childhood and adolescent B-NHL/B-AL.[30,31]

The following table summarizes treatment results from trials of pediatric patients with mature aggressive B-cell lymphoma/leukemia.

Table 2. Treatment results from trials of pediatric patients with mature aggressive B-NHL/B-AL

Trial	No of pts	Risk group	Treatment	Outcome	Reference
LMB 89	52	A	A: 2 courses COPAD no IT injections	A: 5y OS 100% EFS 98% (90-100%)	Patte et al., Blood, 2001[32]
	386	B	B: 2 courses COPAD, 2 courses CYM and 1 course maintenance	B: 5y OS 94% (91-96) and 5y EFS 92% (89-95%)	Patte et al., Blood, 2001[32]
	123	C	COP, COPADM1, COPADM2, CYVE, CYVE, m1, m2, m3,m4	5y OS 85% (78-90%) 5y EFS 84% (77-90%)	Patte et al., Blood, 2001[32]
FABLMB96	132	A	2 courses COPAD, no IT injections	4y OS 99% (96-100%), 4y EFS 98% (94-99%)	Gerrard et al., BJH, 2008[33]
	657 random	B	COP, COPADM1, COPADM2, CYM, CYM, +M1	4y EFS: 91-93% according to random. arm	Patte et al., Blood, 2007[34]
	190 random	C	COP, COPADM1, COPADM2, CYVE, CYVE, m1, m2, m3, m4; randomized trial	4y OS: 79+3% 4y EFS 82+3%; differences according to arms	Cairo et al., Blood, 2007[35]
NHLBFM95	48	R1	R1: courses A, and B	R1: EFS 94±4%,	Woessmann et al., Blood, 2005[36]
	R2: 233 R3: 82	R2/R3	R2: prephase, A; B, A, B randomization to MTX-24h or MTX-4h with 1g/m2 R3: prephase, AA, BB, CC, AA, BB	R2:EFS 94±2% R3: 3y EFS 85±4%	Woessmann et al., Blood, 2005[36]
	142 (40 CNS+)	R4	prephase, AA BB, CC,AA, BB, CC randomization to MTX-24h or MTX-4h with 5 g/m2	R4: 3y EFS 81±3% CNS+: 3y EFS 69±7%	Woessmann Et al., Blood, 2005[36]
AIEOP LNH92	13	R1	2 cycles A and B	OS 100% EFS 100%	Pillon et al., Cancer, 2004[37]
	54	R2	4 cycles of repeated AA and BB	R2: OS 94% EFS 87±9%	Pillon et al., Cancer, 2004[37]
	77	R3	4 cycles of repeated AA and BB; CC in case of residual disease	R3: OS 84% EFS 75±10%	Pillon et al., Cancer, 2004[37]
JACLS NHL 98	13	A	8-day courses of steroids, vincristine, CPM, piarubicin and triple drug IT therapy	A: 6y OS and 6y EFS 100%	Fujita et al.; Leuk Lymph, 2011[38]
	B: 17 C: 21	B and C	8-day courses of steroids, vincristine, CPM, HDMTX, Ara-C, piarubicin and triple drug IT therapy	B: 6y OS and 6y EFS 100% C: OS 85±8% 6y EFS 75±10%	Fujita et al., Leuk Lymph, 2011[38]
	18	D	8-day courses of steroids, vincristine, CPM, HDMTX, Ara-C, piarubicin, etoposide and triple drug IT	D: OS 77±10% 6y EFS 66±11%	Fujita et al., Leuk Lymph, 2011[38]

TCCSG NHLB9604	3	A	3 steroid courses , VCR, CPM, HDMTX, Ara-C, etoposide, double drug IT	A: OS 100% EFS 66.7±27.2%	Kikuchi et al., Leuk Lymph, 2008[39]
	B: 25 C: 46	B and C	6 courses of steroids, VCR/VDS, CPM, HDMTX, Ara-C, epirubicin, etoposide triple/double drug IT	B: OS 100% EFS 95.8±4.1% C: OS 87±5% EFS 78±6%	Kikuchi et al., Leuk Lymph, 2008[39]
	17	D	7 courses of steroids, VCR/VDS, CPM, HDMTX, Ara-C, epirubicin, etoposide triple/double drug IT	D: OS 82±9% EFS 82±9%	Kikuchi et al., Leuk Lymph, 2008[39]
Inter-B-NHL 2010	310 random	B/C	B: prephase, COPADMx2, CYMx2± Rituximab C: prophase, COPADMx2, CYVEx2 ± Rituximab, maintenance	Rituximab arm: 1y EFS 94.2%, control arm: 1y EFS 81.5%	Minard et al., (abstract), 2016[40]

In the last two decades, two treatment strategies for mature aggressive B-NHL/B-AL in childhood and adolescence have dominated in Europe due to their almost similar results; the French LMB trials and the BFM (Germany, Austria and Switzerland) studies. However, they differ in terms of stratification of patients into risk groups, treatment intensity and the choice, dose and schedule of drugs used. Therefore, in preparation of the international cooperative trial Inter-B-NHL 2010, a retrospective comparison of the French LMB treatment regimen and the BFM regimen was performed. For that purpose, both groups shared data on patient characteristics, treatment and outcome, and performed statistical analyses. Both analyses revealed the same results: 691 patients from the LMB-group (07/96-12/05) and 935 patients from the BFM-group (04/96-12/05) were included. A total of 42 patients with PMLBCL were excluded. The 4-year EFS rates were 90% in the LMB and 89% in the BFM trials, respectively. Considering the higher risk patients with stage III disease and an initially high LDH serum level (> twice the upper normal value, or > 500 U/L), stage IV and B-AL, 4-year EFS rates were 85% (n=366) in the LMB and 84% (n=393) in the BFM trials. It was concluded that the two regimens developed in parallel since 1981 and using the same drugs, obtain similar results.[41]

B-NHL BFM trials

In the NHL-BFM 95 trial a randomized design was used to test whether the rate of mucositis grade III/IV can be reduced by shortening the methotrexate (MTX) infusion duration from 24 hours to 4 hours without impairing failure free survival. Final analyses of the trial revealed that, for patients with both low tumor volume (R1/R2) and advanced stages of B-NHL/B-AL (R3/R4), a shorter MTX infusion period (4 hours) is associated with decreased mucositis rates. However, it also led to a significant increase in relapses for patients with advanced stages. In conclusion, the MTX infusion rate could be reduced for patients with low tumor burden, but not for patients with an advanced stage of mature aggressive B-NHL/B-AL.[42] The subsequent observational trial, B-NHL BFM 04, aimed to confirm the results of the NHL-BFM 95 trial through an optimized and consistent treatment strategy. The B-NHL BFM 04 trial recommended chemotherapy as administered in the NHL-BFM 95 trial including a reduced MTX infusion period of four hours for patients with a low tumor burden. Compared to the NHL-BFM 95 trial, B-NHL BFM 04 differed by the following points:

1. For CNS-positive patients, the use of an Ommaya reservoir was no longer recommended and was substituted by a regimen of intensified intrathecal (IT) treatment via lumbar puncture. Interim analyses showed no increase in toxicity or relapses for this group of patients.
2. For patients with primary mediastinal B-cell lymphoma (PMLBL), the findings of a BFM-analysis of the NHL-BFM 86, 90 and 95 trials were used to modify the treatment recommendation[43]: the analyses had shown that the initial LDH level might be a relevant prognostic parameter. In addition, it was observed that most relapses occurred in patients who received less than six courses of chemotherapy. In conclusion, the number of courses was increased to a minimum of six with a MTX dosage of 1g/m^2 over 24 hours, and the LDH level of 500 U/L was introduced as a cut-off level for further intensification: For patients with an initial LDH level >500 U/L the MTX dosage was increased

to 5g/m^2 over 24 hours and a seventh course of chemotherapy was added. However, this treatment modification did not lead to a respective increase in EFS. Therefore, the protocol was amended by the note that participating centers should contact the NHL-BFM study center for cases of newly diagnosed PMLBL for individual consultation (i.e., DA-R-EPOCH)

3. During patient recruitment, in 2010 the protocol was amended by a modified regimen of oxazaphosphorines. The interval between administrations was reduced from 24 hours to 12 hours without modification of the absolute doses nor the number of administrations (constant cumulative dose). This amendment was based on pharmacokinetic data and the experience of the French LMB group with administration of oxazaphosphorines in 12-hourly intervals.[44-46] Although the NHL-BFM 04 results are not published, there is no evidence for increased toxicity with shorter intervals.

In parallel to the B-NHL BFM 04 trial, the NHL-BFM group started a phase II study, B-NHL BFM Rituximab to evaluate the efficacy of rituximab in pediatric patients with mature aggressive B-NHL/B-AL. The expected response rate of 65% after a five-day window of monotherapeutic rituximab was not achieved, neither with one standard dose of 375 mg/m^2 nor with the escalated dose of 700 mg/m^2.[47] However, historical comparisons showed an increase in EFS for at least R3/R4 patients by only adding one dose of rituximab as a window therapy.

The latest B-NHL 2013 treatment protocol of the NHL-BFM and NOPHO groups for mature aggressive B-cell lymphoma and leukemia in children and adolescents, opened in 2017 and differs from B-NHL BFM 04 by the following points with an emphasis on CNS protection and treatment:

1. Patients with B-AL and blasts in the CSF at the time of diagnosis receive 8g/m² methotrexate compared to 5g/m² in previous trials. The rationale for this intensification was arrived at following analyses of the B-NHL BFM 04 trial which showed that 10 out of 32 patients with CNS+ B-AL suffered from relapses, involving CNS in 7/10 cases. EFS for those 32 CSF+ B-AL patients was 53±9% vs 92±5% for 25 CNS+ patients with less than 25% blasts in BM (p=0.0018)[48]. The French LMB group reported favorable results for CNS+ B-NHL/B-AL patients after having increased the dose of methotrexate to 8g/m²[49]. Therefore, it was decided to increase the dose of methotrexate in the first course for CSF+ B-AL patients. The folinic acid rescue is modified accordingly.
2. In the NHL-BFM 95 trial and the B-NHL BFM 04 protocol it was recommended that the intrathecal (IT) triple drug administrations were split in two, but due to poor compliance the B-NHL 2013 protocol no longer recommends splitting the IT drug.
3. For early CNS protection, patients will receive the first intrathecal triple dose during the rituximab window and not during prephase. CNS positive patients will get two intrathecal doses during the rituximab window and one additional dose compared to the B-NHL BFM 04 protocol.

LMB and FAB-LMB trials

Since 1981, the French Society of Pediatric Oncology (SFOP) has conducted several consecutive multi-center LMB studies. The general scheme of the LMB protocols of the studies consisted of:

- a prephase, called COP, with small doses of vincristine, cyclophosphamide and prednisone, to induce good tumor reduction and permit the management of metabolic or other acute problems without myelosuppression,
- an intensive induction phase starting one week later with two consecutive courses of COPADM based on fractionated high dose (HD) cyclophosphamide and HD MTX combined with vincristine, adriamycin (doxorubicin) and prednisone,
- two consolidation courses, based on 5 days of continuous infusion Cytarabine (Ara-C). CNS prophylaxis is given by HD MTX and intrathecal injections of MTX + Ara-C,
- maintenance therapy, consisting of monthly 5 days courses with the previously used drugs, which varied along the studies and was progressively shortened.

The major conclusions of the LMB studies were as follows:

- During the first 2 **LMB 81 and 84** studies[50,51], EFS of CNS-negative advanced stages increased to 75-80%, while duration of treatment was progressively reduced from 12 to 5 courses, resulting in a decrease in toxicity. CNS prophylaxis by HD MTX (3 g/m² in 3h infusion) and IT MTX was efficient with a CNS relapse rate <2%. It was shown that partial remission (with documented viable cells in the residual mass) after 3 courses had a poor outcome, but patients could be salvaged by treatment intensification, and that the absence of tumor reduction after COP was indicative of a poor prognosis (EFS = 29%).
- In the **LMB 86** study, a higher dose of MTX (8 g/m² in 4 h), HD Ara-C [CYVE courses = combination of Ara-C (in continuous infusion and HD) with VP16], and repeated triple IT were introduced, resulting in an increase of EFS from 19% to 75% for patients with initial CNS involvement[52]. This intensified strategy was also beneficial to patients with B-AL as those without CNS involvement could achieve an EFS of about 90%. To note, in the LMB 86 trial, patients received cranial irradiation.

- The following **LMB 89** study[53] was designed defining three risk groups which received treatment of progressive intensity: Group A patients (resected stage I and resected abdominal stage II) received only 2 courses of COPAD without IT nor HDMTX. Group B patients (not eligible for group A or C) received a five-course treatment identical to the short arm of the LMB 84 protocol: after the prephase, 2 courses of COPADM followed by 2 courses of CYM (HD MTX with Ara-C in 5 days continuous infusion) and a maintenance (m1) phase similar to COPADM with lower doses of cyclophosphamide. Group C patients (with CNS involvement and B-AL with >70% of blasts in bone marrow) received the most intensive treatment of 8 courses similar to that of the LMB 86 protocol: after the prephase, 2 courses of COPADM with HD MTX at a dose of 8g/m², 2 courses of CYVE and 4 maintenance courses (m1 to m4). Cranial irradiation was only given to patients with CNS involvement. Treatment was further intensified for group B patients who did not respond to COP and any patient with residual viable cells after the consolidation phase, by "switching" to the group C regimen. EFS was similar within different histological subgroups exceeding 90%. Prognostic factors included LDH level, non-response to COP and CNS disease.
- The next study, **FAB LMB 96**, was a randomized international trial with the participation of the SFOP, the United Kingdom Children's Cancer Study Group (UKCCSG) and the Children's Cancer Group (CCG) from the USA.[44-46]
It was an attempt to further reduce the total drug dosage especially that of cyclophosphamide to avoid sterility in boys, to reduce treatment duration, and to suppress cranial irradiation in patients with initial CNS involvement. The study confirmed the excellent outcome of group A with a larger number of patients [n=132 patients, 4-year EFS of 98.3%, 4-year OS of 99.2%].[46] For the patients of group B, being good responders to COP and in complete remission after the third course of chemotherapy, treatment was decreased to 4 courses delivering only 3.3 g/m² of cyclophosphamide and 120 mg/m² of doxorubicin.[34] In group C, the diminution by 1/3 of the HD Ara-C dose and by half of the VP16 dose led to a decrease in the EFS of 10%, so the trial was closed after the third interim analysis (Cairo, 2007).[45]
Based on the results of the NHL-BFM 95 study, in the observational study **SFOP/SFCE LMB 2001/2003**, the possibility of improving the outcome of patients with CNS positive or with a poor response to COP was tested by increasing the duration of the HD MTX infusion from 4 to 24h. Preliminary results indicated an improved outcome for these patients. However, toxicity, especially the mucositis rate and intensity, appeared higher than seen with the shorter infusion time.
- The international **Inter-B-NHL Ritux 2010** trial was designed to test, in a randomized way, whether the addition of rituximab to LMB backbone chemotherapy can improve EFS in patients with high risk B-NHL or B-AL. The first interim analysis conducted in August 2015 showed that 1-year EFS in the rituximab arm was superior compared to the control arm (94.2% vs 81.5%, *p*=0.006) and the randomization was stopped in favor of the Rituximab arm in November 2015 following the recommendations of the Independent Data Monitoring Committee.[40] With a three-year survival rate exceeding nearly 95%, the results were outstanding. This study changed the international treatment benchmark in young patients with advanced B-cell non-Hodgkin lymphoma and B-AL. As Burkitt lymphoma is a rare disease (~1000/1200 new cases/year in Europe and in the USA), 12 countries had to collaborate to answer this question. The randomised phase III Inter-B-NHL Ritux 2010 trial was conducted between December 2011 and November 2015 and involved 328 patients, aged between 2 and 18 years, treated in 176 centres distributed over four continents (Europe, North America, Australia and Asia). When rituximab was administered with chemotherapy, almost 95% of children and adolescents with advanced Burkitt lymphoma or B-AL were alive and disease-free after more than three years.

1.3 Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) in children and adolescents accounts for 10-15% of childhood and adolescent NHL.[54] More than 90% of systemic ALCL in children carry an oncogenic reciprocal translocation involving chromosome band 2p23 resulting in the fusion of the *anaplastic lymphoma kinase* (*ALK*) gene to one of several partners. The most common ALK fusion protein is nucleophosmin (NPM)-ALK resulting from the t(2;5)(p23;q35) translocation occurring in 90% of ALK-positive ALCL.[55,56] ALK fusion proteins play an essential role in lymphomagenesis and the survival of tumor cells.
The following table summarizes treatment results from trials of pediatric patients with ALCL.

Table 3. Treatment results from trials of pediatric patients with ALCL

Trial	Stratification	Patients	Courses	Therapy duration	pEFS	Reference
		(N)	(N)	(months)	(%)	
HM 90/91	No	82	10	8	64±10	Brugieres et al. 1998[57]
NHL-BFM 90	stage	89	6	5	76±5	Seidemann et al. 2001[58]
UKCCSG-NHL 9001/9002/9003	stage	55	8	6	59±12	Williams et al. 2002[59]
APO-POG9315	No	86	17	12	72±6	Laver et al. 2005[60]
CCG-5941	No	86		12	68±11	Lowe et al. 2009[61]
LNH-92	No	34	n.a.	24	65±8	Rosolen et al. 2005[62]
ALCL 99	clinical RF	352	6	5	73±4	Brugieres et al. 2009[63]

Given that ALCL was not recognised as a distinct form of NHL until 1989, most patients prior to this time would have been treated as having B- or T-cell NHL. The NHL-BFM 90 study was the first trial to include a treatment arm specifically for ALCL, based on the previous NHL-BFM studies. In recent trials, with very different first-line chemotherapy regimens concerning duration of treatment, number and cumulative doses of drugs, astonishingly similar EFS rates of about 65-75% have been achieved.[57-64] The non-randomized NHL-BFM 95 study aimed towards therapy improvement for high-risk patients identified by clinical and pathological parameters (data not published). Intensification with high-dose Ara-C combined with etoposide and high-dose methotrexate did not lead to a higher EFS compared to the historical control of the NHL-BFM 90 trial. In the largest multinational trial ALCL-99, the NHL-BFM 90 strategy with the lowest cumulative drug doses and shortest time of therapy duration was chosen as a backbone.[58] With more than 400 children included from 15 countries, an EFS of 73% was achieved.[63,65] The primary objectives of the ALCL-99 study were to test whether intrathecal therapy could be safely omitted when high-dose MTX was applied in a higher dose but as a shorter infusion and whether intensification with the addition of vinblastine in high-risk patients during intensive courses and maintenance could improve EFS. The results showed no difference in the EFS of patients treated with 1g/m^2 MTX infused over 24h with IT therapy, compared to those patients who received 3g/m^2 MTX over 3h without IT therapy. However, the toxicity of the 24h-infusion was significantly higher.[63] Therefore, since 2006 all ALCL patients except those with isolated skin disease and CNS-involvement are treated with 3 courses (completely resected stage I) or 6 courses (all other patients) of chemotherapy containing 3g/m^2 MTX infused over 3h without IT therapy. Addition of vinblastine showed no significant benefit in comparison to patients not receiving vinblastine, with relapse being delayed rather than prevented.[65] Although ALK fusions are attractive targetable genetic aberrations, no ALK tyrosine kinase inhibitor has been tested yet in front-line therapy for pediatric ALCL patients except for an ongoing US trial.

2. PATIENT GROUPS AND DIAGNOSTICS

This document applies to the following patients:
- newly diagnosed NHL, including mature B-NHL/B-AL, LBL and ALCL
- <18 years old at diagnosis.

Special modifications may be required for patients with:
- underlying chromosomal breakage syndrome, severe immunodeficiency or HIV infection
- previous organ transplantation
- previous malignancy or previous chemotherapy/radiotherapy
- other pre-existing disease prohibiting standard therapy or systemic corticosteroid treatment
- during pregnancy or lactation
- simultaneous participation in a clinical study
- other subtypes of NHL such as PMLBCL, pediatric-type follicular lymphoma, marginal zone lymphoma, Large B-cell lymphoma (LBCL) with *IRF4/MUM* rearrangement and peripheral T-cell lymphoma

2.1 Diagnostic Criteria

2.1.1 Classification of NHL

NHL subtypes are classified according to the WHO classification system which was updated in 2008 and 2016.[66] The following table summarizes the NHL subtypes occurring in children. Further NHL subtypes described in the WHO classification are only seen in rare cases or never in children. Especially in such cases, reference pathology by experienced pediatric hematopathologists should be performed to confirm the diagnosis.

Table 4. WHO classification system for NHL (2016)

Acute leukemias of ambiguous lineage	
Acute undifferentiated leukemia	9801/3
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*	9806/3
Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged	9807/3
Mixed phenotype acute leukemia B/myeloid, NOS	9808/3
Mixed phénotype acute leukemia T/myeloid, NOS	9809/3
Precursor lymphoid neoplasms	
B lymphoblastic leukemia/lymphoma	
B lymphoblastic leukemia/lymphoma, NOS	9811/3
B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*	9812/3
B lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL* rearranged	9807/3
B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1* (*ETV6-RUNX1*)	9814/3
B lymphoblastic leukemia/lymphoma with hyperdiploidy	9815/3
B lymphoblastic leukemia/lymphoma with hypodiploidy	9816/3
B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*	9817/3
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)*	9818/3
T lymphoblastic leukemia/lymphoma	
T lymphoblastic leukemia/lymphoma	9837/3
Mature B-cell neoplasms	
Pediatric nodal marginal zone lymphoma	9699/3
Pediatric follicular lymphoma	9690/3
Diffuse large B-cell lymphoma (DLBCL), NOS	9680/3
T-cell/histiocyte rich large B-cell lymphoma	9688/3
Primary DLBCL of the CNS	9680/3
DLBCL associated with chronic inflammation	9680/3
Primary mediastinal (thymic) large B-cell lymphoma	9679/3
ALK positive large B-cell lymphoma	9737/3
Burkitt lymphoma	9687/3

B-cell lymphoma unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma	9680/3
B-cell lymphoma unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma	9596/3
Mature T-cell and NK-cell neoplasms	
Systemic EBV-positive T-cell lymphoproliferative disease of childhood	9724/3
Extranodal NK/T-cell lymphoma, nasal type	9719/3
Enteropathy-associated T-cell lymphoma	9717/3
Hepatosplenic T-cell lymphoma	9716/3
Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Primary cutaneous CD30 positive lymphoproliferative disorders	
Lymphomatoid papulosis	9718/1
Primary cutaneous anaplastic large cell lymphoma	9718/3
Primary cutaneous gamma-delta T-cell lymphoma	9726/3
Peripheral T-cell lymphoma, NOS	9702/3
Anaplastic large cell lymphoma, *ALK* positive	9714/3
Anaplastic large cell lymphoma, *ALK* negative	9702/3

2.1.2 Diagnostic approach and surgery

To establish a diagnosis of NHL, the least invasive procedure for taking a biopsy should be performed. However, fine-needle or trocar needle biopsy is usually not recommended because tissue specimens gained by these methods is frequently insufficient for complete characterization of the disease. Therefore, needle biopsy should be restricted to those situations where more invasive intervention is contraindicated.

In cases of suspected lymphoma, all options to establish the diagnosis should be considered before surgery is performed, i.e., examination of blood and bone marrow (BM) and/or examination of pleural effusion/ascites when applicable. In cases of malignant effusions and/or significant bone marrow infiltration (>20% blasts) the diagnosis can be established by means of cytomorphology (cytospin preparations), immunophenotyping of cells by flow cytometry and genetics.

Only if the diagnosis cannot be established using these simple techniques should surgery be performed. The main principles of a surgical approach to NHL include:

- The primary goal of surgery is to achieve the biopsy for diagnosis. Complete resection should not be conducted, unless it is possible without any risks or functional losses for the patient.
- The most peripheral lesion should be chosen for biopsy, i.e., in the case of a mediastinal tumor, extra-thoracic manifestations should be carefully sought for a biopsy.
- Although surgery should be a minimally invasive procedure, the material gained by surgery should be adequate for comprehensive characterization of the disease. The biopsy material should not be completely fixated in formol, because most important biological investigations would then be prohibited. Pre-surgical planning for processing of the tumor material should be made by a team consisting of a surgeon, pediatric oncologist and pathologist.
- In patients with mature B-NHL, the resection status is one of several parameters for risk group stratification. Therefore, the resection status “completely resected” has to be evaluated and confirmed carefully. The relevance of this information should be discussed with the surgeon prior to the surgery. As mentioned above, complete resection should not be the intention of surgery, if it cannot be achieved without any risks or functional losses for the patient.

Relevant exceptional cases:

- For patients with a **mediastinal tumor** other diagnostic procedures (pleural puncture, etc.) should be performed to avoid surgery. If there is no pleural effusion and there are no lymphoblasts in the bone marrow, a thorough search should be carried out for extrathoracic manifestations which can be used for a biopsy. Note that with intubation, respiratory failure can occur due to tracheal edema and tracheal compression post-operatively. If intubation is performed for such patients, it is recommended to electively continue ventilation after surgery and to start cytoreductive therapy immediately. Extubation should be postponed until significant shrinking of the tumor is achieved by cytoreductive therapy. Patients with a critically large mediastinal tumor with clinical symptoms of respiratory distress should not be treated surgically and any distressing diagnostic procedure must be questioned depending on the clinical situation. In such a situation, cytoreductive therapy with prednisone and, if necessary, cyclophosphamide should be started immediately without any

diagnostic procedure but a full blood count. Surgery should be postponed until clinical stabilization is achieved.

- In patients with **pericardial effusion**, initiation of the cytoreductive prephase prior to puncture should be carefully assessed in collaboration with colleagues from the intensive care unit.
- In cases of suspected **pB-LBL based only on BM investigation**, the diagnosis has to be confirmed by biopsy and histology of another tumor lesion, because sometimes hematogones cannot be distinguished from pB-LBL blasts based on currently available morphologic and immunophenotypic methods.

2.1.3 Processing of tissue and cell specimens

The table below summarizes specimens that can be tested to confirm a diagnosis of NHL, as well as the relevant processing and the required investigation.

Table 5. Tissue and cell specimens

Material	Processing	Investigation
Lymphoma	Formol fixated	Histology Immunohistochemistry
	Shock frozen	Molecular genetics Cell banking
Tumor touch imprints	10 slides, unstained	Cytomorphology, FISH
Bone marrow (2 sites)	20 ml with EDTA	Molecular genetics/MDD; Cytogenetics Cell banking
	6 slides, unstained	Cytomorphology
	5 ml with heparin*	Immunology**
Bone marrow biopsy	Formol fixated	Histology, Immunohistochemistry
Liquor/ Cerebrospinal fluid (CSF)	3 cytospin preparations, unstained	Cytomorphology
Blood	15-20 ml with EDTA	Molecular genetics/MDD Cell banking
Pleural effusion/ Ascites	10 cytospin preparations, unstained	Cytomorphology
	As much as possible with heparin*	Cytogenetics Molecular genetics/MRD Cell banking
	5 ml with heparin*	Immunology

MDD, minimal disseminated disease
* use heparin without stabilizer, recommendation: 50 IU heparin/1ml effusion.
** only in cases of ≥ 20% lymphoma cells in the bone marrow

2.1.4 Initial diagnostics

Important information:

- For valid risk group assessment, initial lumbar puncture (LP) and bone marrow puncture (BMP) are essential. Initial LP and BMP should be performed *prior to protocol treatment administration and not later than 24 hours after steroid administration*.
- If there is either severe respiratory insufficiency and/or vena cava compression syndrome all further diagnostics (except for blood tests), and especially invasive diagnostic procedures, should be postponed until clinical stabilization is achieved. Cytoreductive therapy with prednisone ± cyclophosphamide should be started immediately.

- In patients with chromosomal breakage syndrome (ataxia-telangiectasia, Nijmegen breakage syndrome or other) CT and X-ray should be replaced by MRI.

Initial diagnostics and staging include the following investigations:

- Complete history including B-symptoms (fever greater than 38°C for >7 days, drenching night sweats, unintentional weight loss of >10% of normal body weight over a period of 6 months or less).
- Detailed physical examination including Lansky/Karnofsky performance status
- Bone marrow aspirate from two sites: morphology, immunology and genetics (if >20% blasts)
- Bone marrow biopsy: immunohistochemistry
- Lumbar puncture: cell count, cytospin preparation for morphology (independently from cell count), glucose and protein
- Assessment of cardiac function by echocardiography (assessment of shortening and ejection fraction)
- In pubertal boys, sperm banking should be discussed and, if performed, sperm should be cryopreserved before starting chemotherapy; in pubertal girls and women, possibilities for fertility preservation should be discussed and if applicable and wished, performed before starting chemotherapy

The following imaging procedures should be performed:

- Ultrasound of the abdomen, lymph nodes, testis and thorax (to exclude pleural or pericardial effusions)
- MRI of the involved region if applicable
- Chest x-ray, posterior-anterior
- Cranial MRI, in case of symptoms or lymphoma manifestations close to the CNS
- In cases of mediastinal involvement: chest CT or MRI with contrast
- In cases of suspected bone lesions: X-ray and/or MRI (and bone scintigraphy)
- In cases of neurological signs suggesting spinal cord compression: spinal MRI
- Data regarding PET-CT are limited at present. It is only recommended for initial staging, if it does not delay the start of treatment. Staging has to be defined by the findings seen on the high-resolution CT and not from PET.

Laboratory investigations:

- Full blood count, differential and platelet count, reticulocytes, blood smears
- Electrolytes, urea, creatinine, uric acid, calcium, phosphorous, albumin
- SGOT, SGPT, gamma GT, bilirubin
- LDH level
- Hemostasis/coagulation tests
- HIV antibody test
- Serum level of HB Ags, anti-HBs antibodies, anti-HBc antibodies, IgG, IgM; Viral serology including EBV, CMV, according to local/national standards.
- Pregnancy test for girls/female adolescents with signs of puberty

2.1.5 Definition of organ involvement

- *Central nervous system involvement*

For **LBL** three patterns of CNS involvement may be distinguished:

Type 1: CNS-negative
- no identifiable blasts in the CSF of cytospin-preparations (independent of cell number)
- no cerebral/medullary infiltrates detected on cranial/spinal MRI
- no cranial nerve palsy that cannot be explained by extradural lesions

Type 2:
- < 5 cells/µl CSF, but definite blasts in the cytospin preparation.

Type 3: CNS-positive
- > 5 cells/µl in the CSF and morphologically identifiable blasts in the CSF on cytospin preparations
- and/or cerebral/medullary infiltrates on cranial/spinal MRI
- and/or a cranial nerve palsy that cannot be explained by extradural lesions

In **NHL subtypes other than LBL,** CNS involvement is defined by at least one of the following criteria:

- morphologically identifiable blast(s) in CSF irrespective of cell count (in doubtful cases, molecular genetics or FISH might help to diagnose blast cells in patients with ALCL or Burkitt lymphoma).
- cerebral/medullary infiltrates detected by cranial/spinal MRI or CT
- cranial nerve palsy that cannot be explained by an extradural lesion

- *Bone marrow involvement*

In **LBL,** bone marrow involvement is diagnosed if there are ≥5% and <25% blasts in BM aspiration smears. In cases of ≥ 25% lymphoblasts (FAB L1/L2) in the BM a diagnosis of ALL should be made.
Exception: In patients with a focal bone lesion and BM infiltration of more than 25% blasts in this lesion, but less than 25% blasts in all other puncture sites, a diagnosis of LBL should be considered.
In **ALCL,** bone marrow involvement is defined as the presence of morphologically identifiable tumor cells.
In **mature aggressive B-cell lymphoma,** bone marrow involvement is diagnosed if there are ≥5% blasts in the BMP. Minimal disseminated disease below a cytological threshold diagnosed by molecular methods in bone marrow or blood, i.e., in patients with ALCL or BL, is not considered bone marrow involvement.
Definition of Burkitt leukemia (B-AL): If there are ≥25% FAB-L3 blasts in the bone marrow and the chromosomal rearrangements t(8;14), t(8;22) or t(2;8), or monoclonal immunoglobulins are present on ≥25% of malignant cells, B-AL should be diagnosed.

- *Mediastinal involvement*

Mediastinal involvement should be confirmed by MRI or CT scan. The histopathological diagnosis of LBL should, whenever possible, be corroborated by biopsy of other organs, such as peripheral lymph nodes.

- *Lung involvement*

Lung involvement should be confirmed by chest CT. The histopathological diagnosis should, whenever possible, be corroborated by biopsy of other organs, such as peripheral lymph nodes.

- *Bone involvement*

Bone involvement is diagnosed if there are bone lesions on x-ray or MRI, provided the diagnosis of LBL is already histologically established. If the bone lesion is the only manifestation of a suspected LBL, a bone biopsy must be performed.

- *Testicular involvement*

Testicular involvement is diagnosed clinically as the presence of a painless enlargement of one or both testicles, provided the diagnosis of NHL is established otherwise. If painless enlargement of one or both testicles is the only detectable lesion, a biopsy must be performed.

- *Skin involvement*

To confirm suspected skin involvement, a biopsy is necessary if it is relevant for diagnosis or risk stratification (i.e., for ALCL). Skin infiltration by continuous tumor growth arising from an involved lymph node or a soft tissue tumor is not considered primary skin involvement.

2.1.6 Staging

Staging is performed according to International the Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS)[67] and St. Jude's Staging System[68] based on bone marrow puncture/biopsy, lumbar puncture and imaging procedures.

Table 6. International Pediatric Non-Hodgkin Lymphoma Staging System

Stage	Criteria for extent of disease
I	• Single tumor with exclusion of the mediastinum and abdomen
II	• Single extranodal tumor with regional node involvement • ≥ Two nodal areas on the same side of diaphragm • Primary gastrointestinal tract tumor (usually in ileocecal area), ± involvement of associated mesenteric nodes, that is completely resectable (if there are malignant ascites or extension of tumor to adjacent organs, it should be regarded as stage III)
III*	• ≥ Two extranodal tumors above and/or below the diaphragm • ≥ Two nodal areas above and below the diaphragm • Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic) • Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except primary GI tract tumor [usually in ileocecal region] ± involvement of associated mesenteric nodes that is completely resectable) • Any paraspinal or epidural tumor, regardless of whether other sites are involved • A single bone lesion with concomitant involvement of extranodal and/or non-regional nodal sites
IV	• Any of the above findings with initial involvement of CNS (stage IV CNS), BM (stage IV BM), or both (stage IV combined) based on conventional methods

Table 7. St. Jude's Staging System

Stage	Criteria for extent of disease
I	• A single tumor (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
II	• A single tumor (extranodal) with regional node involvement • Two or more nodal areas on the same side of the diaphragm • Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm • A primary gastrointestinal tumor usually in the ileocecal area with or without involvement of associated mesenteric nodes only, grossly completely resected
III*	• Two single tumors (extranodal) on opposite sides of the diaphragm • Two or more nodal areas above and below the diaphragm • All primary intra-thoracic tumors (mediastinal, pleural, thymic) • All extensive primary intra-abdominal disease • All paraspinal or epidural tumors regardless of other tumor site(s)
IV	• Any of the above with initial CNS and/or bone marrow involvement

*in addition, relevant for mature B-NHL: multilocular bone disease

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3. TREATMENT DETAILS

3.1 Lymphoblastic lymphoma

Patients with precursor lymphoid neoplasms are treated according to the ALL-type treatment regimen (see Appendix A).

Risk Group Stratification

High Risk Group (HR):
• All stages of T-LBL including mixed lineage LBL (T/myeloid or T/B)
• pB-LBL including mixed lineage LBL (B/myeloid) with stage III and IV disease
• all LBL with an unknown CNS and/or BM status

Standard risk group (SR):
• pB-LBL including mixed lineage LBL (B/myeloid) with stage I and II disease

Protocol elements

Protocol Ia
- Prednisone/prednisolone 60 mg/m^2/d divided into 3 doses from day 1 to 28 and then tapering over 9 days halving the dose every 3rd day.
- Vincristine 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on days 8, 15, 22 and 29 (4 doses).
- Daunorubicin 30 mg/m^2/d IV over 1 hour on days 8, 15, 22 and 29 (4 doses). Echocardiography before the 1st and 3rd doses.
- PEG asparaginase 2500 IU/m^2/d IV (maximum 3750 IU) over 2 hours on days 12 and 26 (2 doses).
- Intrathecal chemotherapy according to age:
  - CNS negative: Methotrexate IT on days 1, 12, 18, 27 and 33 (5 doses).
  - CNS positive: Methotrexate – Ara-C - Prednisolone IT twice weekly until blast clearance in CSF and on scheduled days 1, 12, 18, 27 and 33 (5 doses).

age	methotrexate IT [mg]	cytarabine IT [mg]	prednisolone IT [mg]
< 1 year	6	16	4
1 - < 2 years	8	20	6
2 - < 3 years	10	26	8
≥ 3 years	12	30	10

Protocol Ib
Protocol Ib requires an adequate clinical condition without infection, normal creatinine levels, granulocytes ≥ 0.5 x 10^9/l and platelets ≥ 50 x 10^9/l.
- Cyclophosphamide 1000 mg/m^2/d IV over 1 hour on days 36 and 64 (with hydration and MESNA for cystitis-prophylaxis). The second dose of cyclophosphamide requires WBC ≥ 1 x 10^9/l, granulocytes ≥ 0.3 x 10^9/l and platelets ≥ 50 x 10^9/l.
- 6-mercaptopurine 60 mg/m^2/d orally from days 36 to 63 (28 doses).
- Cytarabine 75 mg/m^2/d IV over 15 minutes, 4 blocks for 4 days (16 doses) on days 38-41, 45-48, 52-55 and 59-62. Each block requires a WBC ≥ 0.5 x 10^9/l and platelets ≥ 50 x 10^9/l.
- Intrathecal chemotherapy according to age:
  CNS negative: Methotrexate IT on days 45 and 59 (2 doses).
  CNS positive: Methotrexate - Ara-C - Prednisolone IT on days 45 and 59 (2 doses).

Protocol M
Protocol M requires an adequate clinical condition without infection, normal renal function, no urinary obstruction, SGOT/SGPT < 10 x upper normal limit, bilirubin < 3 x upper normal limit with normal direct bilirubin, granulocytes ≥ 0.5 x 10^9/l and platelets ≥ 50 x 10^9/l.
- 6-mercaptopurine 25 mg/m^2/d orally from days 1 to 56 (56 doses).
- Methotrexate 5 g/m^2 IV over 24 hours with hydration and alkalization (urine pH ≥ 7.0) before, during and until levels < 0.2 µmol/l are reached on days 8, 22, 36 and 50 (4 doses).

  - Folinic acid rescue (15 mg/m2/6 hours IV) beginning 42 hours after commencing the MTX infusion and until levels < 0.2 µmol/l are reached. MTX levels would be assessed at 24, 36, 42, 48 and 54 hours (or more if excretion is prolonged) (see Folinic acid dose adjustments according to MTX levels, 3.5.8).
- Intrathecal chemotherapy according to age (during MTX infusion):
  - CNS negative: Methotrexate IT on days 8, 22, 36 and 50 (4 doses).
  - CNS positive: Methotrexate - Ara-C - Prednisolone IT on days 8, 22, 36 and 50 (4 doses).

Protocol II
All high-risk patients receive a *re-intensification* phase (protocol II).

Protocol IIa requires an adequate clinical condition without infection, granulocytes ≥ 0.5 x 10^9/l and platelets ≥ 50 x 10^9/l. Vincristine and doxorubicin doses may be postponed if the WBC < 0.5 x 10^9/l or granulocytes < 0.2 x 10^9/l until blood count recovery.
- Dexamethasone 10 mg/m^2/d divided into 3 doses from days 1 to 21 and then tapering over 9 days halving the dose every 3rd day.
- Vincristine 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on days 8, 15, 22 and 29 (4 doses). It can be omitted in cases of severe neuropathy.
- Doxorubicin 30 mg/m^2/d IV over 1 hour on days 8, 15, 22 and 29 (4 doses). Echocardiography is mandatory before the 1st and 3rd doses.
- Intrathecal chemotherapy according to age:
  - CNS negative: Methotrexate IT on days 1 and 18 (2 doses).
  - CNS positive: Methotrexate - Ara-C - Prednisolone IT on days 1 and 18 (2 doses).

Protocol IIb requires an adequate clinical condition without infection, normal renal function, granulocytes ≥ 0.5 x 10^9/l and platelets ≥ 50 x 10^9/l.
- Cyclophosphamide 1000 mg/m^2/d IV over 1 hour on day 36 (with hydration and MESNA for cystitis-prophylaxis).
- 6-thioguanine 60 mg/m^2/d orally from days 36 to 49 (14 doses).
- Cytarabine 75 mg/m^2/d IV over 15 minutes, 2 blocks for 4 days (8 doses) on days 38-41 and 45-48. Each block requires a WBC ≥ 0.5 x 10^9/l and platelets ≥ 50 x 10^9/l.
- Intrathecal chemotherapy, dose according to age:
  - CNS negative: Methotrexate IT on days 38 and 45 (2 doses).
  - CNS positive: Methotrexate - Ara-C - Prednisolone IT on days 38 and 45 (2 doses).

Maintenance
Maintenance usually starts 2 weeks after completion of protocol M for pB-LBL/mixed lineage (B/myeloid) patients with limited disease (stage I + II) and 2 weeks after completion of protocol II for all other patients. Maintenance requires an adequate clinical condition, without infection, absence of progressive disease, SGOT/SGPT < 10 x upper normal limit, bilirubin < 3 x upper normal limit with normal direct bilirubin, granulocytes ≥ 0.5 x 10^9/l and platelets ≥ 50 x 10^9/l.

Maintenance chemotherapy includes:
- 6-mercaptopurine (6-MP) 50 mg/m^2/d orally in the evening.
- Methotrexate (MTX) 20 mg/m^2/d orally in the evening without milk, once a week.
- CNS positive: intrathecal chemotherapy with Methotrexate, Ara-C and Prednisolone, dose according to age, for 4 doses every three weeks.

Maintenance 6-MP and MTX doses should be adjusted upwards to obtain a total white blood cell count of between 1.5 and 3 x 10^9/l, with granulocytes ≥ 0.5 x 10^9/l, lymphocytes ≥ 0.3 x 10^9/l and platelets ≥ 50 x 10^9/l. In general, doses of the two drugs should be kept at the same ratio. The dose ratio of 6-MP:MTX should usually be 2.5:1. For dosing in cases of homozygous TPMT-deficiency, please refer to 6-Mercaptopurine and 6-Thioguanine in section 3.5.7.

Treatment should be reduced or stopped if:
• Myelosuppression: WBC < 1.5 x 10^9/l, granulocytes < 0.5 x 10^9/l, lymphocytes < 0.3 x 10^9/l or platelets < 50 x 10^9/l.
• Febrile infections: During infection course, and at least until afebrile for 1 day and in good general condition.

• Liver toxicity: SGOT/SGPT >10 -20 x UNL and rising (steady high levels can be tolerated) and/or bilirubin > 3 x UNL.
• Mucositis: This is usually related to MTX so usually it is only necessary to reduce the MTX dose.
• Radiological pulmonary changes consistent with methotrexate pneumonitis: MTX therapy should be interrupted.

Patients receive maintenance therapy for a total of 24 months therapy duration calculated from the first day of the cytoreductive prephase.

3.2 Mature aggressive B-cell lymphoma/ leukemia

3.2.1 Therapeutic groups and treatment schemes according to the NHL-BFM concept:

Patients are stratified into four risk groups, depending on the stage of disease, the initial LDH serum level and the status of resection. Patients with initial CNS involvement represent the subgroup R4 CNS+ in the R4 risk group. The following table shows treatment stratification for mature aggressive B-NHL and B-AL (see Appendix B).

Table 8. Risk group stratification for mature aggressive B-NHL according to the BFM concept

Risk group	Resection status	Stage and initial serum LDH level
R1	Complete	
R2	Incomplete	Stage I, II; stage III and LDH < 2 x ULN
R3	Incomplete	stage III and LDH > 2 x ULN but < 4 x ULN stage IV/B-AL and LDH < 4 x ULN and CNS negative
R4	Incomplete	stage III and LDH ≥ 4 x ULN stage IV/B-AL and LDH ≥ 4 x ULN and CNS negative
R4 CNS+	Incomplete	stage IV/B-AL and CNS positive

- **R1: A^4 - B^4**
- **R2: P - A^4 - B^4 - A^4 - B^4**
- **R3-R4 CNS negative: P - AA^{24} - BB^{24} - CC - AA^{24} - BB^{24} - CC (only in R4)**
- **Patients with CNS-involvement (stage IV mature B-NHL): $P_{(IT)}$ - $AAZ1^{24}$ - $BBZ1^{24}$ - CC - $AAZ2^{24}$ - $BBZ2^{24}$ - CC**
- **Patients with CNS-involvement (mature B-AL with initial blast in CSF): $P_{(IT)}$ - AA^8Z1 - $BBZ1^{24}$ - CC - $AAZ2^{24}$ - $BBZ2^{24}$ - CC**

When to start each cycle:
Minimal interval between two courses (not for P and 1st course): 16 days, granulocytes > 0.5 x 10^9/l and platelets > 50 x 10^9/l and an adequate clinical condition without infection, normal creatinine and creatinine clearance, GOT/GPT ≤ 5xULN and bilirubin ≤ 3xULN.

Prephase P
- Dexamethasone 5 mg/m^2/d in three doses on days 1 and 2 and 10 mg/m^2/d in three doses on days 3, 4 and 5.
- Cyclophosphamide 200 mg/m^2/d IV over 1 hour on days 1 and 2 with hydration and MESNA for cystitis-prophylaxis.

Prephase $P_{(IT)}$ for R4 CNS+ patients
- Dexamethasone 5 mg/m^2/d in three doses on days 1 and 2, and 10 mg/m^2/d in three doses on days 3, 4 and 5.
- Cyclophosphamide 200 mg/m^2/d IV over 1 hour on days 1 and 2 with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on day 1.

Cycles A^4
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 5.
- Vincristine (not in R1) 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push, or less than 15 minutes on day 1 (1 hour before MTX application).
- Cytarabine (ARA-C) 150 mg/m^2/d IV over 1 hour on days 4 and 5 (before VP-16).

- Etoposide (VP-16) 100 mg/m^2/d IV over 2 hours on days 4 and 5 (after ARA-C).
- Methotrexate (MTX) 1 g/m^2 IV over 4 hours on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after MTX infusion.
    - Folinic acid rescue (15 mg/m^2/6 hours) beginning 42 hours after the start of the MTX infusion and until at least 54 hours if adequate levels at 48 h (< 0.25 µmol/L) are observed. MTX levels would be analysed at least at 24, (36), 42 and 48 hours of MTX infusion (see Folinic acid dose adjustments according to MTX levels in section 3.5.8).
- Ifosfamide 800 mg/m^2/d IV over 1 hour from days 1 to 5 with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on day 2 (if needed it can be given on day 1).

Cycles AA[24]
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 5.
- Vincristine (not in R1) 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (1 hour before MTX application).
- Cytarabine (ARA-C) 150 mg/m^2/d IV over 1 hour on days 4 and 5 (before VP-16).
- Etoposide (VP-16) 100 mg/m^2/d IV over 2 hours on days 4 and 5 (after ARA-C).
- Methotrexate (MTX) 5 g/m^2 IV over 24 hours on day 1 (1/10 of the total dose over 30 minutes and 9/10 of the total dose as a continuous infusion over 23 ½ hours) with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after MTX infusion.
    - Folinic acid rescue (first dose 30 mg/m^2 and then 15 mg/m^2/6 hours) beginning 42 hours after the start of MTX infusion and at least until 54 hours if adequate levels at 48 h (< 0.4 µmol/L). MTX levels would be done at least at 24, (36), 42 and 48 hours of MTX infusion (see Folinic acid dose adjustments according to MTX levels in 3.5.8).
- Ifosfamide 800 mg/m^2/d IV over 1 hour from day 1 to 5 with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on day 2 (if needed it can be given on day 1).

Cycles AAZ1[24] for CNS positive patients:
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 6.
- Vincristine (not in R1) 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (1 hour before MTX application).
- Cytarabine (ARA-C) 150 mg/m^2/d IV over 1 hour on days 4 and 5 (before VP-16).
- Etoposide (VP-16) 100 mg/m^2/d IV over 2 hours on days 4 and 5 (after ARA-C).
- Methotrexate (MTX) 5 g/m^2 IV over 24 hours on day 1 (1/10 of the total dose over 30 minutes and 9/10 of the total dose as a continuous infusion over 23 ½ hours) with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after the MTX infusion.
    - Folinic acid rescue (first dose 30 mg/m^2 and then 15 mg/m^2/6 hours) beginning 42 hours after the start of the MTX infusion and until at least 54 hours if adequate levels at 48 h (< 0.4 µmol/L) are observed. MTX levels would be analysed at least at 24, (36), 42 and 48 hours of MTX infusion (see Folinic acid dose adjustments according to MTX levels in 3.5.8).
- Ifosfamide 800 mg/m^2/d IV over 1 hour from days 1 to 5 with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on days 2, 4 and 6.

Cycles AA8Z1 for CNS positive mature B-AL patients
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 6.
- Vincristine (not in R1) 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (1 hour before MTX application).
- Cytarabine (ARA-C) 150 mg/m^2/d IV over 1 hour on days 4 and 5 (before VP-16).
- Etoposide (VP-16) 100 mg/m^2/d IV over 2 hours on days 4 and 5 (after ARA-C).
- Methotrexate (MTX) 8 g/m^2 IV over 24 hours on day 1 (1/5 of the total dose over 30 minutes and 4/5 of the total dose as a continuous infusion over 23 ½ hours) with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after the MTX infusion.
    - Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until the MTX levels are < 0.15 µmol/L. MTX levels should be analysed at least every 24 hours from 48 hours after the MTX infusion (see Folinic acid dose adjustments according to MTX levels in 3.5.8).
- Ifosfamide 800 mg/m^2/d IV over 1 hour from days 1 to 5 with hydration and MESNA for cystitis-prophylaxis.

- Intrathecal chemotherapy according to age on days 2, 4 and 6.

Cycles AAZ2 for CNS positive patients
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 6.
- Vincristine (not in R1) 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (1 hour before MTX application).
- Cytarabine (ARA-C) 150 mg/m^2/d IV over 1 hour on days 4 and 5 (before VP-16).
- Etoposide (VP-16) 100 mg/m^2/d IV over 2 hours on days 4 and 5 (after ARA-C).
- Methotrexate (MTX) 5 g/m^2 IV over 24 hours on day 1 (1/10 of the total dose over 30 minutes and 9/10 of the total dose as a continuous infusion over 23 ½ hours) with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after MTX infusion.
  - Folinic acid rescue (first dose 30 mg/m^2 and then 15 mg/m^2/6 hours) beginning 42 hours after the start of MTX infusion and until at least 54 hours if adequate levels are observed at 48 h (< 0.4 µmol/L). MTX levels should be analysed at least at 24, (36), 42 and 48 hours of the MTX infusion (see Folinic acid dose adjustments according to MTX levels in 3.5.8).
- Ifosfamide 800 mg/m^2/d IV over 1 hour from days 1 to 5 with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on days 2 and 6.

Cycles B^4
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 5.
- Vincristine 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (1 hour before MTX application).
- Doxorubicin 25 mg/m^2/d IV over 1 hour on days 4 and 5.
- Methotrexate (MTX) 1 g/m^2 IV over 4 hours on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after MTX infusion.
  - Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until levels < 0.2 µmol/l are reached. MTX levels should be analysed at least every 24 hours (see Folinic acid dose adjustments according to MTX levels in section 3.5.8).
- Cyclophosphamide 200 mg/m^2/12 hours IV over 15 minutes from days 2 to 4 (5 doses) with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on day 2 (if needed it can be given on day 1).

Cycles BB^{24}
- Dexamethasone 10 mg/m^2/d in two doses from day 1 to 5.
- Vincristine 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (1 hour before MTX application).
- Doxorubicin 25 mg/m^2/d IV over 1 hour on days 4 and 5.
- Methotrexate (MTX) 5 g/m^2 IV over 24 hours on day 1 (1/10 of total dose over 30 minutes and 9/10 of total dose as continuous infusion over 23 ½ hours) with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after MTX infusion.
  - Folinic acid rescue (first dose 30 mg/m^2 and then 15 mg/m^2/6 hours) beginning 42 hours after the start of MTX infusion and at least until 54 hours if adequate levels at 48 h (< 0.4 µmol/L). MTX levels would be done at least at 24, (36), 42 and 48 hours of MTX infusion (see Folinic acid dose adjustments according to MTX levels in 3.5.8).
- Cyclophosphamide 200 mg/m^2/12 hours IV over 15 minutes from day 2 to 4 (5 doses) with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on day 2 (if needed it can be given on day 1).

Cycles BBZ1
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 6.
- Vincristine 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (1 hour before MTX application).
- Doxorubicin 25 mg/m^2/d IV over 1 hour on days 4 and 5.
- Methotrexate (MTX) 5 g/m^2 IV over 24 hours on day 1 (1/10 of the total dose over 30 minutes and 9/10 of the total dose as a continuous infusion over 23 ½ hours) with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after the MTX infusion.
  - Folinic acid rescue (first dose 30 mg/m^2 and then 15 mg/m^2/6 hours) beginning 42 hours after the start of the MTX infusion and at least until 54 hours if adequate levels are observed at 48 h

(< 0.4 µmol/L). MTX levels should be analysed at least at 24, (36), 42 and 48 hours of the MTX infusion (see Folinic acid dose adjustments according to MTX levels in 3.5.8).
- Cyclophosphamide 200 mg/m^2/12 hours IV over 15 minutes from days 2 to 4 (5 doses) with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on days 2, 4 and 6.

Cycles BBZ2
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 6.
- Vincristine 1.5 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (1 hour before MTX application).
- Doxorubicin 25 mg/m^2/d IV over 1 hour on days 4 and 5.
- Methotrexate (MTX) 5 g/m^2 IV over 24 hours on day 1 (1/10 of the total dose over 30 minutes and 9/10 of the total dose as a continuous infusion over 23 ½ hours) with hydration and alkalization (urine pH ≥ 7.0) before, during and until at least 48 hours after the MTX infusion.
  - Folinic acid rescue (first dose 30 mg/m^2 and then 15 mg/m^2/6 hours) beginning 42 hours after the start of the MTX infusion and at least until 54 hours if adequate levels are observed at 48 h (< 0.4 µmol/L). MTX levels should be analysed at least at 24, (36), 42 and 48 hours of the MTX infusion (see Folinic acid dose adjustments according to MTX levels in 3.5.8).
- Cyclophosphamide 200 mg/m^2/12 hours IV over 15 minutes from days 2 to 4 (5 doses) with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on days 2 and 6.

Cycles CC
- Dexamethasone 20 mg/m^2/d in three doses from days 1 to 5.
- Vindesine 3 mg/m^2/d (maximum 5 mg each dose) IV in push or less than 15 minutes on day 1 before cytarabine.
- Cytarabine 3 g/m^2/12 hours IV over 3 hours on days 1 and 2 (4 doses). Artificial tears every 6-8 hours and vitamin B_6 at 150 mg/m^2/12 hours should be given.
- Etoposide 100 mg/m^2/12 hours IV over 2 minutes from days 3 to 5 (5 doses).
- Intrathecal chemotherapy according to age on day 5.
-

3.2.2 Therapeutic groups and treatment schemes according to the European Intergroup for Children Non-Hodgkin Lymphoma (EICNHL) concept[40]:

(see Appendix C.)

Table 9. Risk group classification for B-NHL/B-AL according to the EICNHL concept

Risk group	Resection status	Stage and initial serum LDH level
A	complete	
B I	Incomplete	stage I, II and III with LDH < 2 UNL and good response to COP (> 20% reduction)
B II (high risk)	Incomplete	B I with poor response to COP (< 20% reduction) stage III with LDH > 2 x ULN and stage IV CNS negative
C1	Incomplete	stage IV CNS positive and CSF negative B-AL CNS negative
C3	Incomplete	B-AL CNS positive (with blasts)

- **A: COPAD - COPAD**
- **B-I: COP - COPADM - COPADM – CYM – CYM**
- **B-II: COP - R-COPADM - R-COPADM - R-CYM – R-CYM**
- **C1: COP - R-COPADM - R-COPADM2 - R-CYVE - R-CYVE - m1 - m2**
- **C3: COP - R-COPADM - R-COPADM2 - R-IT-CYVE-MTX - R-IT-CYVE - m1 - m2**

When to start each cycle:
After the first cycle, or pre-phase (COP) and first cycle, each course starts as soon as an adequate clinical condition without infection, granulocytes > 1 x 10^9/l and platelets > 100 x 10^9/l is accomplished. This usually happens at around 18 to 21 days after the cycle except between CYVE cycles in positive CNS patients, which is around the 28th day.
- The Rituximab dose of day -2 could start as soon as granulocytes ≥ 0.5 x 10^9/l without infection.

- The second cycle usually starts around 18 days after the first one; it is recommended to be no less than 16 days or more than 21 days later. If the clinical condition does not allow starting treatment before 21 days, a "waiting COP" or at least a rituximab interphase would be an option to avoid treatment discontinuation.

COPAD
- Prednisone 60 mg/m^2/d in two or three doses from days 1 to 5 and reduce it until a stop on day 10.
- Vincristine 2 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on days 1 and 6.
- Cyclophosphamide 250 mg/m^2/12 hours IV over 30 minutes on days 1, 2 and 3 (6 doses) with hydration and MESNA for cystitis-prophylaxis.
- Doxorubicin 60 mg/m^2/d IV over 1 hour on day 1.

COP
- Prednisone 60 mg/m^2/d in two or three doses from days 1 to 7.
- Vincristine 1 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1.
- Cyclophosphamide 300 mg/m^2/d IV over 15 minutes on day 1 with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age:
  - B-I patients receive three dugs intrathecally on day 1
  - B-II patients receive two drugs intrathecally (methotrexate and hydrocortisone) on day 1.
  - Patients with positive CNS (C1 and C3) receive three dugs intrathecally on days 1, 3 and 5 with folinic acid rescue (15 mg/m^2/12 hours) on days 2 and 4.

Age	methotrexate IT [mg]	hydrocortisone IT [mg]	*cytarabine IT [mg] B-I (without rituximab) C1 and C3 patients CYM it in B-II*
< 1 year	8	8	15
1 - < 2 years	10	10	20
2 - < 3 years	12	12	25
≥ 3 years	15	15	30

Rituximab window R for high risk patients (prior to each course except the COP pre-phase)
- Rituximab 375 mg/m^2/d IV on days -2 and 1 for R-COPADM/R-COPADM2 and on day 1 for R-CYM and R-CYVE.

COPADM (1st and 2nd) in CNS negative patients (B)
- Prednisone 60 mg/m^2/d in two or three doses from days 1 to 5 and reduce until the stop on day 9.
- Vincristine 2 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (before MTX application).
- Methotrexate (MTX) 3 g/m^2 IV over 3 hours on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and until MTX elimination is reached.
  - Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached. MTX levels should be analysed and Folinic acid dose adjustments conducted according to section 3.5.8.
- Doxorubicin 60 mg/m^2/d IV over 1 hour on day 2.
- Cyclophosphamide 250 mg/m^2/12 hours IV over 30 minutes on days 2, 3 and 4 (6 doses) with hydration and MESNA for cystitis-prophylaxis.
- Intrathecal chemotherapy according to age on days 1 and 6:
  - B-I patients: three drugs intrathecally
  - B-II patients: two drugs intrathecally (methotrexate and hydrocortisone)

COPADM (1) in CNS positive patients (C1 and C3)
- Prednisone 60 mg/m^2/d in two or three doses from days 1 to 5 and reduce until the stop on day 9.
- Vincristine 2 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (before the MTX application).
- Methotrexate (MTX) 8 g/m^2 IV over 4 hours on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and until MTX elimination is reached.

  - Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached. MTX levels should be analysed and Folinic acid dose adjustments conducted according to section 3.5.8.
- Doxorubicin 60 mg/m^2/d IV over 1 hour on day 2.
- Cyclophosphamide 250 mg/m^2/12 hours IV over 30 minutes on days 2, 3 and 4 (6 doses) with hydration and MESNA for cystitis-prophylaxis.
- Triple intrathecal chemotherapy according to age on days 2, 4 and 6.

COPADM2 in CNS positive patients (C1 and C3)
- Prednisone 60 mg/m^2/d in two or three doses from days 1 to 5 and reduce until the stop on day 9.
- Vincristine 2 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (before the MTX application).
- Methotrexate (MTX) 8 g/m^2 IV on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and until MTX elimination is achieved.
  - *In C1*: 8 g/m^2 IV over 4 hours. Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached.
  - *In C3*: 8 g/m^2 IV over 24 hours (1/5 of the total dose over 30 minutes and 4/5 of the total dose as a continuous infusion over 23 ½ hours). Folinic acid rescue (15 mg/m^2/6 hours) beginning 36 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached.
  - MTX levels should be analysed and Folinic acid dose adjustments performed according to section 3.5.8.
- Doxorubicin 60 mg/m^2/d IV over 1 hour on day 2.
- Cyclophosphamide 500 mg/m^2/12 hours IV over 30 minutes on days 2, 3 and 4 (6 doses) with hydration and MESNA for cystitis-prophylaxis.
- Triple intrathecal chemotherapy according to age on days 2, 4 and 6.

CYM
- Methotrexate (MTX) 3 g/m^2 IV over 3 hours on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and until MTX elimination is achieved.
  - Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached. MTX levels should be analysed and Folinic acid dose adjustments conducted according to section 3.5.8.
- Cytarabine (ARA-C) 100 mg/m^2/d IV over 24 hours from days 2 to 6 (5 doses).
- Intrathecal chemotherapy according to age:
- Intrathecal chemotherapy according to age on days 1 and 6:
  - B-I patients: three drugs intrathecal
  - B-II patients: two drugs intrathecal: methotrexate and hydrocortisone on day 2 and Hydrocortisone and Cytarabine on day 7.

CYVE
- Cytarabine (ARA-C) 50 mg/m^2/d IV over 12 hours from days 1 to 5 (5 doses, 8 pm to 8 am).
- High dose – commence Cytarabine 3 g/m^2/d IV over 3 hours at the end of the 12 hour cytarabine infusion on days 2 to 5 (4 doses, from 8 am to 11 am). Artificial tears every 6-8 hours and vitamin B_6 at 150 mg/m^2/12 hours should be given.
- Etoposide (VP-16) 200 mg/m^2/d IV over 2 hours from days 2 to 5 (after ARA-C).
- * *For positive CNS*: intrathecal chemotherapy according to age with methotrexate and hydrocortisone on day 1.
- * *For positive CNS ONLY in 1st CYVE*: Methotrexate (MTX) 8 g/m^2 IV on day 18 (while granulocytes > 0.5 x 10^9/l and platelets > 50 x 10^9/l and transaminases < Nx10) with hydration and alkalization (urine pH ≥ 7.0) before, during and until MTX elimination is achieved.
  - *In C1*: 8 g/m^2 IV over 4 hours. Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached.
  - *In C3*: 8 g/m^2 IV over 24 hours (1/5 of the total dose over 30 minutes and 4/5 of the total dose as a continuous infusion over 23 ½ hours). Folinic acid rescue (15 mg/m^2/6 hours) beginning 36 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached.

  MTX levels should be analysed and Folinic acid dose adjustments conducted according to section 3.5.8.
- * *In positive CNS ONLY in 1st CYVE*: Triple intrathecal chemotherapy according to age the day after MTX.

m1
- Prednisone 60 mg/m^2/d in two or three doses from days 1 to 5 and reduce until the stop on day 9.
- Vincristine 2 mg/m^2/d (maximum 2 mg each dose) IV in push or less than 15 minutes on day 1 (before MTX application)
- Methotrexate (MTX) 8 g/m^2 IV on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and until MTX elimination is achieved.
  - *In C1*: 8 g/m^2 IV over 4 hours. Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached.
  - *In C3*: 8 g/m^2 IV over 24 hours (1/5 of the total dose over 30 minutes and 4/5 of the total dose as a continuous infusion over 23 ½ hours). Folinic acid rescue (15 mg/m^2/6 hours) beginning 36 hours after the start of the MTX infusion and until MTX levels < 0.15 µmol/L are reached.

  MTX levels should be analyzed and Folinic acid dose adjustments conducted according to section 3.5.8.
- Doxorubicin 60 mg/m^2/d IV over 1 hour on day 2.
- Cyclophosphamide 500 mg/m^2/d IV over 30 minutes on days 2 and 3 with hydration and MESNA for cystitis-prophylaxis.
- Triple intrathecal chemotherapy according to age the day after MTX.

m2
- Cytarabine (ARA-C) 50 mg/m^2 as a subcutaneous injection every 12 hours from days 1 to 5 (10 doses).
- Etoposide (VP-16) 150 mg/m^2/d IV over 90 minutes from days 1 to 3 (after ARA-C).

3.3 Anaplastic Large Cell Lymphoma

For patients with ALCL, therapy is stratified according to which organs are involved and the postoperative stage. The following therapeutic groups exist:

- Isolated skin disease: no treatment is necessary after staging. “Wait and watch”.
- Stage I ALCL: completely resected stage I: **prephase (V) + AM - BM - AM courses**
- All other systemic ALCL: **prephase (V) + AM - BM - AM - BM - AM - BM courses**
- Patients with CNS-involvement: chemotherapy according to CNS-positive mature B-NHL followed by cranial radiotherapy (in patients > 1 year). Patients between 1 and 2 years of age receive 12 Gy and patients ≥ 2 years old, 18 Gy.

Chemotherapy courses should start while granulocytes are ≥ 0.5 x 10^9/l, platelets ≥ 50 x 10^9/l and rising, and patients are clinically well and free of infection (around 21 days) (see Appendix D).

Prephase V
- Dexamethasone 5 mg/m^2/d in one dose on days 1 and 2 and 10 mg/m^2/d in two doses on days 3, 4 and 5.
- Cyclophosphamide 200 mg/m2 IV over 1 hour on days 1 and 2 (with hydration and MESNA for cystitis-prophylaxis).
- Intrathecal chemotherapy according to age on day 1.

Age	methotrexate IT [mg]	cytarabine IT [mg]	prednisolone IT [mg]
< 1 year	6	16	4
1 - < 2 years	8	20	6
2 - < 3 years	10	26	8
≥ 3 years	12	30	10

Cycles AM
- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 5.
- Methotrexate (MTX) 3 g/m2 IV over 3 hours on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and for at least 69 hours after the MTX infusion commences.
  - Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion. MTX levels should be conducted at least every 24 hours (see Folinic acid dose adjustments according to MTX levels in section 3.5.8).
- Ifosfamide 800 mg/m^2/d IV over 1 hour from days 1 to 5 (with hydration and MESNA for cystitis-prophylaxis).

- Cytarabine (ARA-C) 150 mg/m^2/d IV over 1 hour on days 4 and 5 (before VP-16).
- Etoposide (VP-16) 100 mg/m^2/d IV over 2 hours on days 4 and 5 (after ARA-C).

Cycles BM

- Dexamethasone 10 mg/m^2/d in two doses from days 1 to 5.
- Methotrexate (MTX) 3 g/m^2 IV over 3 hours on day 1 with hydration and alkalization (urine pH ≥ 7.0) before, during and for at least 69 hours after the MTX infusion has commenced.
  - Folinic acid rescue (15 mg/m^2/6 hours) beginning 24 hours after the start of the MTX infusion and until levels < 0.2 µmol/l are reached. MTX levels should be analysed at least every 24 hours (see Folinic acid dose adjustments according to MTX levels in section 3.5.8).
- Cyclophosphamide 200 mg/m^2/d IV over 1 hour from days 1 to 5 with hydration and MESNA for cystitis-prophylaxis.
- Doxorubicin 25 mg/m^2/d IV over 1 hour on days 4 and 5.

3.4 Assessments during treatment

Table 10. Assessments during treatment for LBL, B-NHL and ALCL

	Physical examination + full blood count +/-blood chemistry	**Lumbar puncture and CSF cytospin**	**BM aspirate**	**Imaging**	**Echocardiography**
Lymphoblastic Lymphoma					
Diagnosis	X	X	X	X	X
D +12	X	X[1]			X *(before 3rd dose of daunorubicin)*
D + 33	X	X[1]	X[2]	X[3] *Reduction of at least 35% of the initial volume*	
Before protocol M	X	X[1]	X[2]	X[3]	X *(before daunorubicin)*
Before protocol II *reintensification*	X			X[3]	X *(before 1st and 3rd dose of doxorubicin)*
Before maintenance	X			X[3]	
Maintenance 1st year (4-weekly)	X			X[3]	
Maintenance 2nd year (8-weekly)	X			X[3]	
End of therapy	X			X[3]	
Mature B-NHL and Burkitt leukemia					
Diagnosis	X	X	X	X	X
Before every course	X	X[1]			
Before 2nd course	X	X[1]	X[2]		X
Before 3rd course	X	X[1]	X[2]	X[3]	
End of therapy	X			X[3]	
Anaplastic Large Cell Lymphoma					
Diagnosis	X	X[4]	X	X	X
Before every course	X			X[3]	
After prephase	X		X		
Before 2nd course	X		X[2]		X
Before 3rd course	X				X
Before 6th course	X		X		X
End of therapy	X			X[3]	X

The interpretation and responsibility of the use of this ESCP guidance document lies fully with the user (please see full disclaimer on page 6)

[1] In cases of CNS+ or suspected progression. [2] In cases of initial bone marrow involvement or suspected progression. [3] In cases of CR, the indication for imaging and type of exploration are conducted according to the decision of the responsible physician. MRI and CT are preferred to radiography and ultrasound until CR is achieved, then follow up with radiography and ultrasound are sufficient. [4] ALCL with CNS+ are extremely rare, treatment and follow up are conducted according to the CNS+ mature B-NHL protocol followed by radiotherapy.

3.5 Summary of known adverse events, treatment recommendations and dose modifications

Acute side effects such as nausea and vomiting, weight loss, alopecia, uncomplicated myelosuppression, mucositis or infections during or after chemotherapy are expected toxicities. Late side effects include an increased risk of secondary malignancies, cardiac events, infertility and premature menopause.
Specific adverse events and their treatment recommendation and treatment adjustment if required, are listed below:

3.5.1 Cyclophosphamide

Drug-specific toxicities: Acute side effects include hemorrhagic cystitis, myelosuppression, syndrome of inappropriate antidiuretic hormone secretion (SIADH), fluid retention, renal tubular damage, kidney defects, nausea, vomiting, stomatitis, alopecia and an increased infection risk. Late effects include: sterility, second malignancies including leukemia or bladder cancer, cardiotoxicity and gustatory disorders.

In cases of hematuria, micro- or macrohematuria, dysuria or stranguria during or after cyclophosphamide, increase the fluid intake (usually from 3 l/m^2/24 hours to 4-4.5 l/m^2/24 hours) with fluid balance, intensification of MESNA dose and give pain killers until resolution. For subsequent doses, ensure hydration before starting cyclophosphamide treatment.

3.5.2 Cytarabine (ARA-C)

Drug-specific toxicities:

Low-dose cytarabine: myelosuppression, oro-intestinal mucositis, nausea, vomiting, oral ulceration, fever (not infectious), arthralgia, myalgia, bone pain, erythema, enteritis, bowel wall necrosis, diarrhoea, ulceration and bleeding, alopecia, flu-like syndrome, flushes and liver function disorders.

High-dose cytarabine (3 000 mg/m2): cerebellar toxicity, keratoconjunctivitis (can be prevented with prednisolone eye drops 3x/day), gastrointestinal toxicity with diarrhoea, mucositis and vomiting (may be more severe than with the low dose), tachycardic arrhythmia, somnolence, cerebellar ataxia, aphasia, nystagmus, peripheral neuropathy. Pulmonary toxicity is uncommon, but may present with unexplained breathlessness. High incidences of Streptococcus viridans pneumonia have been reported.

In cases of neurotoxicity (nystagmus and/or ataxia) the infusion needs to be stopped immediately and the patient should not receive further doses of HD-cytarabine. High-dose vitamin B6 (150 mg/m^2/single dose i.v. or p.o., 2x daily) is recommended to prevent neurotoxicity.

In cases of grade 3-4 keratoconjuntivitis, therapy should be paused until recovery/improvement.

3.5.3 Daunorubicin and Doxorubicin (Adriamycin)

Drug-specific toxicities: Acute and chronic cardiotoxicity with cardiomyopathy, local necrosis if extravasation occurs, myelosuppression (pancytopenia), phlebitis, oro-intestinal mucosal toxicity, mucosal ulceration, nausea, vomiting, alopecia, fatigue, headache, rise of transaminases and alkaline phosphatase.

Heart function has to be examined by electrocardiogram (ECG) and a cardiac ultrasound scan for examination of left ventricular function (LVF) before starting and regularly thereafter (usually every two doses). In cases where significant impairment compared to the initial findings (left ventricular shortening fraction (LV-SF) are measured at <30% repeatedly or the ejection fraction is <50%), patients should not

receive further doses of daunorubicin or doxorubicin. Temporary alterations of the ECG do not contraindicate further doses.

Doxorubicin can cause palmar-plantar erythrodysesthesia syndrome which usually only requires conservative management.

CAVE: liver function disorders-delayed degradation and heightened toxicity in cases of significantly reduced liver function.

3.5.4 Dexamethasone, Prednisone and Prednisolone

Drug-specific toxicities: suppression of the hypothalamic-pituitary-adrenal axis leading to Cushing syndrome, diabetes mellitus, obesity, hirsutism, fluid and salt retention, sodium retention, potassium loss, hypertension, irritability and sleep disturbances, pseudotumor cerebri, glycosuria and hyperglycaemia, pancreatitis, seizures and mental instability, gastrointestinal ulcers, myopathy, osteoporosis, cataracts, increased intra-ocular pressure, glaucoma, papilledema, psychological changes (euphoria, depression, especially in reduction). Rise in haemoglobin, erythrocytes, neutrophils and thrombocytes, fall in lymphocytes, with a risk of thromboembolic events and with increased susceptibility to and severity of infections, diminished immune response, opportunistic infections, recurrence of dormant tuberculosis and decreased responsiveness to vaccination and skin tests.

In some studies the incidence of osteopathology (osteoporosis, fractures, premature epiphyseal closure, etc.) has been reported to be increased in patients receiving dexamethasone. Usually no dose reduction is needed for these side effects, and medical care according to local guidelines is required.

In cases of pancreatitis, steroids should be stopped and replaced by a glucocorticoid at a stress dose.

In cases of infection or of clinical adrenal insufficiency after discontinuation of steroids, it may be appropriate to initiate a hydrocortisone substitution.

3.5.5 Etoposide (VP-16)

Drug-specific toxicities: transient hypotension (related to quick infusions), allergic reaction, anaphylaxis, rash, myelosuppression, peripheral neuropathies, arrhythmia, cholestasis, alopecia, mucositis, CNS toxicities, mild bone marrow depression and secondary leukemia, nausea, vomiting, diarrhea, fever, headache, chills, asthenia, hepatotoxicity. Peripheral neuropathy, bronchospasm, coughing and laryngospasm are uncommon as are severe neurological side effects such as seizures, optic neuritis, transient cortical blindness, or pulmonary fibrosis, interstitial pneumonitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, radiation recall dermatitis and hand foot syndrome have been described.

In cases of allergic reaction or hypotension, infusion should be stopped. If it occurs despite a low infusion rate, a change from etoposide (Vepesid®) to etoposidphosphat (Etopophos®) may be indicated, as allergies are usually due to etoposide additives.

3.5.6 Ifosfamide

Drug-specific toxicities: similar to cyclophosphamide, especially nephrotoxicity (Fanconi syndrome), neurotoxicity, tubular nephropathy, renal excretion dysfunction, nausea, vomiting, haemorrhagic cystitis, convulsions and secondary malignancies.

CNS-symptoms (encephalopathy with confusion, somnolence, rarely convulsions and coma) can develop within several hours to days after the start of ifosfamide but usually stop within a few days following discontinuation of ifosfamide. Treatment of neurologic side effects with methylene blue at 1-2 mg/kg every 4-8 hours slowly i.v. over several minutes may contribute to the regression of clinical symptoms. After occurrence of CNS-complications, ifosfamide should be replaced by cyclophosphamide for subsequent cycles (give 25% of the ifosfamide dose).

In cases of hematuria, micro- or macrohematuria, dysuria or stranguria during or after ifosfamide, increase fluid intake (usually from 3 l/m^2/24 hours to 4-4.5 l/m^2/24 hours) with fluid balancing, intensification of the MESNA dose and give pain killers until resolution. For subsequent doses ensure hydration before starting ifosfamide.

3.5.7 6-Mercaptopurine

Drug-specific toxicities: Myelosuppression, nausea, vomiting, stomatitis, diarrhea, hepatotoxicity, hyperuraemia with nephropathy, drug fever, exanthema and pancreatitis.

TPMT- deficiency, a deficit in thiopurine-methyltransferase (TPMT) the enzyme that metabolizes 6-mercaptopurine occurs in 1 of every 300 patients. Patients should be evaluated for TPMT deficiency (with wash-out at 8 weeks following the transfusions) as massive toxicity under standard dose therapy is expected. These patients start therapy at 10% of the standard dose and it is then adjusted to the therapeutic range. About 10% of the population has reduced TPMT function (heterozygote gene carrier or homozygote with mild expression) but dose reduction has not yet been established for these patients.

3.5.8 Methotrexate

Methotrexate administration requires pre-hydration and alkalinisation for at least 2 hours before treatment to achieve a urinary pH ≥ 7 and a urine output of ≥ 100 ml/m^2/h during, after MTX infusion and until achieving adequate levels. Monitoring the fluid balance and administering furosemide if the fluid balance is positive.

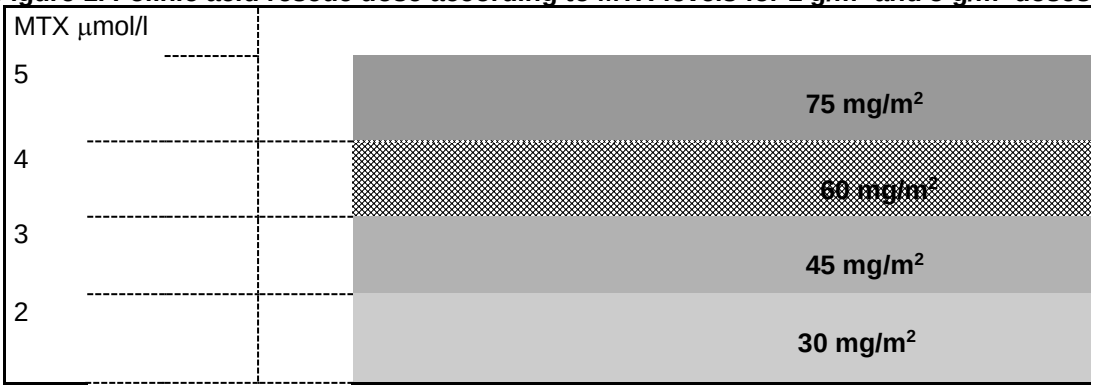
Table 11. Methotrexate levels and standard folinic acid (LCV) rescue:

MTX therapy	1 g/m² over 4 hours		3 or 8 g/m² over 3-4 hours		5 or 8 g/m² over 24 hours	
Time from start of methotrexate (hours)	MTX target µmol/l	LCV mg/m²	MTX target µmol/l	LCV mg/m²	MTX target µmol/l	LCV mg/m²
4	< 200					
24	< 2			15	< 150	
(36)	<1		< 1	15	< 3	15*
42	< 0.4	15	< 0.4	15	≤ 1	30**/ 15
48	< 0.25	15	< 0.25	15	≤ 0.4	15
54		15		15	< 0.25	15
72						

* Starting at 36 hours in 24 hours infusions for B-NHL therapy according to EICNHL; **30 mg/m² in B-NHL therapy according to the BFM scheme

An excretion disorder with delayed elimination may present with diarrhea or intense vomiting during the infusion, a significant rise of serum creatinine 24 hours after starting MTX and a MTX serum concentration over expected levels. If so: increase hydration to 4500 ml/m^2/24 h and measure MTX plasma concentration every 6 hours and give a folinic acid dose according to the following guide:

Figure 1. Folinic acid rescue dose according to MTX-levels for 1 g/m^2 and 5 g/m^2 doses[1]:



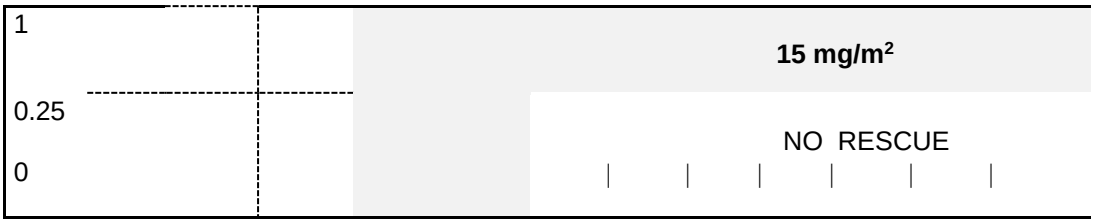


Table 12. Folinic acid doses according to MTX-levels in MTX for doses given over 3 or 4 hours

MTX level µmol/l	<0.2	0.2 – 2	2 – 20	20 - 100	> 100
48 hrs	None	15mg/m² q6h	15mg/m² q6h	10mg/m² q3h	100mg/m² q3h
72 hrs	None	15mg/m² q6h	10mg/m² q3h	100mg/m² q3h	1000mg/m² q3h*
96 hrs	None	15mg/m² q6h	10mg/m² q3h	100mg/m² q3h	1000mg/m² q3h*
120 hrs	None	15mg/m² q6h	10mg/m² q3h	100mg/m² q3h	1000mg/m² q3h*

[1] Diagrams for the adaptation of the folinic acid dose according to MTX-level from B-NHL 2013: protocol of the NHL-BFM and NOPHO study groups for mature aggressive B-cell lymphoma and leukaemia in children and adolescents.

Drug toxicities:
- High doses: neurotoxicity, mucositis, liver dysfunction, myelosuppression, renal failure, mucosal membrane inflammation, dermatitis (erythema, desquamation), nephrotoxicity (enhanced with urine pH<7 and low urine flow in a 24h infusion), ulceration and bleeding, acute and chronic encephalitis, cerebral atrophy, visual disorder and liver toxicity (elevated transaminases, icterus).
- Long-term therapy in low doses: liver fibrosis, pneumonitis, malabsorption and myelosuppression
- Side effects of intrathecal administration: headache, seizures, chemical arachnoiditis, subacute neurotoxicity, necrotizing demyelinating leukoencephalopathy, nausea, vomiting, fever, lethargy and confusion.

CAVE: pooling and/or delayed MTX-excretion in cases of effusion, ileus or limited kidney function
CAVE: prophylactic co-trimoxazole should be stopped 24-48 hours prior to MTX infusion until MTX clearance is achieved.

3.5.9 PEG asparaginase

Drug-specific toxicities: hyperglycaemia, hyperlipidaemia, thrombosis, bleeding, hepatic toxicity, encephalopathy, changes in EEG, vigilance disorder, kidney defects, diarrhea, transient hypothyroidism and hypoparathyroidism. Generally, these side effects resolve with medical management and do not contraindicate the following doses. If needed, asparaginase administration can be delayed until resolution of symptoms.

In cases of allergic reaction (urticarial, laryngospasm, bronchospasm, hypotension, anaphylaxis etc.) patients should not receive more PEG asparaginase as a loss of activity through silent immunologic inactivation is to be expected. Abdominal pain may be an equivalent of an allergic reaction; therefore, measurement of activity and antibodies should be initiated and if insufficient activity is seen, the preparation needs to be changed. Each dose of PEG asparaginase should be replaced in cases of allergy or inactivation by Erwinia asparaginase in doses of 20 000 E/m²/single dose i.v. over one hour or i.m. every two days for the remaining time of the current and following therapy elements. Based on a two-week activity of PEG asparaginase, 7 doses of Erwinia asparaginase replace one dose of PEG asparaginase. Asparaginase activity should be measured before each administration of Erwinia asparaginase.

Severe pancreatitis (grade III or IV) should lead to a discontinuation of asparaginase and any further asparaginase administration is recommended. In case of slight variants (asymptomatic rise of amylase

and/or lipase or with abdominal pain without correlate in imaging and with improvement after few days of conservative therapy) the re-establishment of asparaginase may be discussed.

3.5.10 Rituximab

Patients receiving rituximab treatment require checking of lymphocyte subpopulations and immunoglobulin levels prior to treatment and periodically until normalization.

Known toxicities include: infections, leukopenia, neutropenia, thrombocytopenia, infusion related reactions, hypersensitivity, angioedema, nausea, pruritus, rash, alopecia, fever, chills, asthenia, headache, decreased IgG levels, hyperglycaemia, weight decrease, oedema, paraesthesia, hypoesthesia, dizziness, anxiety, insomnia, lacrimation disorder, conjunctivitis, myocardial infarction, arrhythmia, tachycardia, hypertension, hypotension, bronchospasm, respiratory disease, chest pain, dyspnoea, cough, rhinitis, vomiting, diarrhea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation, urticaria, sweating, myalgia, arthralgia, pain, flushing, malaise, fatigue, shivering, multi-organ failure. Uncommon and very rare toxicities: coagulation disorder, lymphadenopathy, depression, dysgeusia, left ventricular failure, supra-ventricular tachycardia, ventricular tachycardia, angina, myocardial ischemia, bradycardia, asthma, bronchiolitis obliterans, hypoxia, infusion site pain, interstitial lung disease, progressive multifocal leukoencephalopathy (PML), tumour lysis syndrome, cytokine release syndrome, serum sickness, peripheral neuropathy, facial nerve palsy, severe vision loss, heart failure, vasculitis, respiratory failure, gastrointestinal perforation, severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis and renal failure.

3.5.11 Thioguanine

Drug-specific toxicities: myelosuppression, nausea, vomiting, stomatitis, diarrhea, hepatotoxicity, hyperuremia with nephropathy, drug fever, exanthema and pancreatitis.

Patients with TPMT deficiency are at a high risk of developing veno-occlusive disease (VOD) of the liver and so need to be closely monitored.

3.5.12 Vinblastine, Vincristine and Vindesine

Vinca-alkaloids can only be administered intravenously as they are lethal when administered intrathecally. Single dose maximum: 2 mg for Vincristine, 5 mg for Vindesine and 10 mg for Vinblastine.

Drug-specific toxicities**:** Peripheral neuropathy, paresis, myopathy, fever, neuralgic pain, constipation, paralytic ileus, SIADH, constipation, paralytic ileus, cerebral convulsion, myelosuppression, alopecia, cardiovascular complications, photosensitisation, headache, dysphagia, polyuria, dysuria and dysfunction of cranial nerves. Rarely: atrophy of the optic nerve with blindness.

Peripheral neuropathy is a common toxicity, especially after Vincristine. Neuropathic pain should be treated with analgesics. In cases of severe peripheral neuropathy with motor disturbances or paralysis of hands and/or legs, replacement of Vincristine by Vinblastine at a dose of 6 mg/m^2 (10 mg maximum) or Vindesine (3 mg/m2, max 5 mg) might be indicated as they cause less neuropathy.

In cases of hyperbilirubinemia (direct bilirubin > 3.0 mg/dL) therapy adjustments are needed. For Vincristine: 50% of the dose if direct the bilirubin is between 3.1 and 5.0 mg/dL or delayed treatment until improvement if it is over 5 mg/dL.

In cases of neutropenia, < 1x10^9 neutrophils (related to Vinblastine) the dose should be reduced by 30%. It might later be increased to 80% of the initial dose if a sustained rise of over 1x10^9 neutrophils is observed for a month. In cases of < 0.5x10^9 neutrophils or platelets < 50x 10^9/l, vinblastine should be stopped until resolution, and new doses should be given at a 30% reduction.

3.6 Other dose Modifications

3.6.1 Dose modifications for infants

Dosage for systemic chemotherapy should be adjusted in infants:

- ≤ 6 months: 2/3 of the calculated dosage according to BSA
- 7-12 months: ¾ of the calculated dosage according to BSA
- ≥ 1 year: 100% of the calculated dosage according to BSA

The dosage for intrathecal chemotherapy is calculated according to age at the time of its administration.

3.6.2 Dose modifications for obese patients

The need or benefit of drug dose adjustment for obese patients is ambiguous and a clear recommendation cannot be given.

3.6.3 Dose modifications for patients with chromosomal breakage syndromes

It is known that patients with chromosomal breakage syndromes or immunodeficiency are at a higher risk of suffering severe acute toxicity or a diagnosis of secondary malignancies. To date no standard treatment modification has been established for these patients.

3.6.4 Pregnancy

Various chemotherapeutic agents recommended in this guide have known reproductive toxicity; therefore, this treatment cannot be administered to pregnant women. Female patients of childbearing potential (and male patients with a partner of childbearing potential) must agree to use a highly effective contraceptive method (Pearl index <1) throughout treatment and until at least 12 months following the end of chemotherapy.

3.7 Initial Emergencies

Patient management in emergency situations should be performed according to local standards. However, the following recommendations for initial emergencies encountered in patients with NHL should be taken into consideration and be adapted to the specific situation of each patient, modified or extended as the circumstances require.

3.7.1 Mediastinal tumors

The undiagnosed child with a large anterior mediastinal mass may present in many ways. Classical features of superior vena cava obstruction, such as swelling of the upper thorax, head and neck with overlying superficial prominent and distended collateral veins are infrequently observed. More often, an anterior or middle mediastinal mass presents with respiratory and/or neurological symptoms. Posterior mediastinal masses rarely cause superior vena cava or respiratory compromise. Careful clinical assessment should be conducted since airway obstruction has been reported in up to 60% of patients presenting with mediastinal masses. Furthermore, a third of asymptomatic patients show a significant reduction in tracheal dimensions when assessed by chest CT. Not infrequently, pleural and pericardial effusions may be associated with mediastinal masses. Pleural effusions may be bilateral and further compromise the respiratory status.

Management of large mediastinal tumors:

- Under no circumstances should a critically large mediastinal tumor with clinical symptoms of respiratory distress be treated surgically. If a thoracotomy is necessary for sample excision, then debulking of the tumor might be performed in order to reduce the risk of tracheal compression post-operatively.
- chest CT is desirable but can be performed at a later date if the child is likely to be uncooperative or has respiratory compromise (especially orthopnea or oxygen requirement).
- avoid sedation and/or general anesthesia for any further investigations.
- all invasive diagnostic procedures including lumbar puncture, bone marrow aspiration and trephine, should be postponed. Drained fluids are used for diagnosis.
- diagnostic procedures may be undertaken after stabilization of the clinical condition, usually occurring after one or two days.
- baseline blood investigations should be performed as indicated.
- a simultaneously existing pleural effusion should be carefully relieved under local anesthesia. Replace plasma and do not perform long-term drainage, if possible.
- drainage of critical pericardial effusions should be discussed carefully.
- If intubation is performed in these patients, it is recommended to continue ventilation electively after surgery and to start cytoreductive therapy immediately in order to avoid life-threatening respiratory

failure due to tracheal edema and tracheal compression post-operatively. Extubation should be postponed until significant shrinking of the tumor is achieved by cytoreductive therapy.
- cytoreductive therapy with prednisone/prednisolone 60 mg/m²/d and/or cyclophosphamide 100 mg/m²/d should be started immediately. The dosage can be increased depending on clinical progress.
- prevention and treatment of tumor lysis syndrome should be applied.

3.7.2 Prevention and treatment of tumor lysis syndrome (TLS)

Rapid neoplastic cell lysis may occur in NHL patients and can produce metabolic complications including hyperuricemia and hyperphosphatemia. This may already be present at diagnosis due to rapid cell turnover, or occur during induction. Primary complications of TLS include hyperkalemia and hyperphosphatemia with secondary hypocalcemia. Secondary renal dysfunction occurs as the result of a combination of hyperuricemia and hyperphosphatemia with intrarenal deposition of calcium. Renal failure leads to a further rise in serum potassium, urea and creatinine.
Management for the prevention and treatment of TLS should be performed according to local standards. The following information might be considered:
- A central venous line should be inserted for fluid administration and monitoring.
- Sufficient hydration starting at least 6-12 hours before chemotherapy (>3000 ml/m²/d), with appropriate electrolyte supplementation except for potassium, must be provided during chemotherapy. Hydration might be increased to 5000 (7000) ml/m²/24hrs and furosemide 1-10 mg/kg/24 hrs should be added according to the fluid output.
- Monitoring of the fluid balance, blood pressure (hourly), cardiac function (signs of hyperkalemia such as elevation of T waves or widening of the QT interval), respiratory frequencies and body weight (twice daily) are mandatory especially during the main period of lysis, 8-24 hours after the start of chemotherapy.
- Electrolytes, calcium and phosphate should be checked at least every 8 hours.
- If rasburicase (Fasturtec® in Europe) is available it is preferred to allopurinol. The recommended dose is 0.20 mg/kg/d in a 30 min infusion daily during the period of lysis. The dose can be increased as necessary depending on the uric acid level. Do not give allopurinol at the same time. If rasburicase is not available (or contraindicated) then use allopurinol 10 mg/kg/d in 2-3 daily doses to reduce renal tubule urate precipitation.

Indications for hemodialysis
indication for hemodialysis should follow local standards considering the individual course of the patient. The following criteria might serve as guidelines:
- potassium > 7 mmol/l or > 6 mmol/l and increasing, in spite of sufficient diuresis
- phosphate > 10 mg/100 ml (5 mmol/l) or product Ca x P > 6.4 mmol/l
- urine excretion: < 50 ml/m²/hr in spite of furosemide 10 mg/kg/d i.v. and fluid input 130-200 ml/m²/hr
- high-grade or complete urinary tract obstruction on both sides
- pulmonary edema (give oxygen and consider ventilation as immediate measures)
- creatinine > 10x upper normal limit
- uric acid > 10mg/dl (600 µmol/l)

3.8 Supportive Care

The toxic effects of the intensive regimens required for the treatment of NHL, including severe bone marrow depression, stipulate that this treatment should be restricted to institutions familiar with the administration of intensive combination chemotherapy and where the full range of supportive care is available. The following recommendations should be viewed as a general reference and be taken into consideration by the attending physician.

3.8.1 Central lines

The use of central lines is strongly recommended due to the repeated courses of chemotherapy with prolonged hydration. This may have to be postponed in the event of a large mediastinal mass being a contraindication to surgery.

3.8.2 Substitution of blood products

Substitution of blood products should be performed according to local/national standards. For prevention of GvHD use irradiated blood products (minimum of 30 Gy).

3.8.3 Infection prophylaxis and therapy

Prophylaxis: Administration of prophylactic medication against viral, fungal or bacterial infections for prevention of systemic infection is not routinely recommended except for pneumocystis jirovecii prophylaxis.

Pneumocystis jirovecii prophylaxis
All patients should receive a prophylaxis with trimethoprim-sulfamethoxazole (cotrimoxazole) with 5 mg/kg TMP divided into 2 daily doses for 2-3 days a week during the entire phase of chemotherapy to prevent a Pneumocystis jirovecii-pneumonia. Alternatively, pentamidine aerosol inhalation once a month can be administered.

Varicella-Zoster (VZV) exposure prophylaxis
Contact between NHL patients during chemotherapy and individuals with varicella or varicella zoster must be strictly avoided.
Active immunisation of seronegative people in contact with the patient against varicella-zoster virus can reduce the risk of varicella infection of the patient.
After VZV exposure, seronegative NHL patients under intensive treatment should receive varicella-zoster hyperimmunoglobin (1ml/kg i.v.) within 72 (- 96) hours after exposure or aciclovir (40-)80 mg/kg/d in 3-(4) doses starting on the 7th day of incubation for at least 7 days (preferably until day 28 after contact).

Varicella, Herpes zoster and Herpes simplex (manifested illness)
Immunocompromised NHL patients with active disease should receive Aciclovir i.v. 30-45 mg/kg/d i.v. in 3-(4) doses; the duration depends on the severity of infection.

3.8.4 Febrile neutropenia

Febrile neutropenia is defined as an oral/rectal temperature ≥ 38.5°C or 2 measurements >38.0°C within one hour and neutrophils < 0.5 x 10^9/l.

Diagnostics: implementation/supplementation of tests according to the clinical situation

- full blood count, inflammatory indices
- cultures: blood (every catheter channel), stool (incl. clostridium difficile-toxin), urine
- swabs from throat, skin and mucous membrane lesions, anus
- clinical examination and culture of the central line exit-site
- chest x-ray in cases of pulmonary symptoms; in cases of prolonged neutropenia consider a chest CT
- in cases of abnormal pulmonary radiological findings a bronchial lavage should be considered, especially if the patient does not respond to antibiotics
- ultrasound of the abdomen

Treatment: Antibiotic therapy must be customised to the individualized clinical manifestations of each patient and each institution's bacterial colonization and antimicrobial resistance pattern.

- Empirical broad-spectrum antimicrobial monotherapy or combination therapy including aminoglycoside.
- Vancomycin or teicoplanin, if β-lactam-resistant staphyloccocus aureus/staphylococcus mitis species or other virulent gram-positive bacteria (mucositis, catheter, abdominal symptoms) are known or suspected.
- Reserve empirical expansion or change of the antimicrobial therapy regimen only for patients with persistent fever who become clinically unstable.
- Systemic antifungal therapy according to institutional guidelines, if fever is persistent > 4-7 d, or returns after i.v. antibiotics.
- Clindamycin or metronidazol, if anaerobic infection is suspected.
- Clindamycin or rifampicin, in cases of soft tissue infection or osteomyelitis

3.9 Patient Follow-up

The following table provides suggestions for follow-up assessments of NHL patients:

Table 13. Follow-up after treatment

Time from initial diagnosis*	Interval	Examinations
1st year from diagnosis	monthly 6-monthly	physical examination, full blood count imaging of involved sites, hepatic and renal function, LDH, immune reconstitution in cases of Rituximab treatment
2nd year from diagnosis	2-monthly 6-monthly 12-monthly	physical examination, full blood count imaging of involved sites, hepatic and renal function, LDH, immune reconstitution in cases of Rituximab treatment Echocardiography
3rd to 5th year from diagnosis	6-monthly 12-monthly	physical examination, full blood count, immune reconstitution in cases of Rituximab treatment if not already normalized Echocardiography
> 5 years from diagnosis	yearly	physical examination, full blood count, echocardiography, assessment of late effects according to local standards

* or end of maintenance treatment in lymphoblastic lymphoma

3.10 Definition of Events

Death due to initial complications

If a patient dies due to initial complications prior to the start of treatment, or within the beginning of treatment, it is defined as death due to initial complications.

Treatment related mortality

If a patient dies due to complications of treatment (e.g. septicemia) it is defined as treatment related mortality (TRM).

Non-response, progression or relapse

If there is an increase in the diameter of a residual mass which is not obviously a progression/relapse it is recommended that the examination is repeated within a short interval. Diagnosis of progressive disease or relapse must be proven by biopsy and histology, except where it can be established by a simpler procedure, e.g. by examination of the bone marrow or malignant effusions. In cases of progressive disease, the initial diagnostic and staging procedures should be repeated.

Non-response, progression or relapse in patients with LBL

Non-responders are patients with less than 35% volume response/regression at day 33, and/or persistence of >5% blasts in the bone marrow and/or persistence of blasts in the CSF at day 33. In such cases, the NHL-BFM study center might be contacted. If a non-response is confirmed, these patients might be treated according to protocols for high risk ALL. Local irradiation may also be considered.

Usually progressive disease is defined as an event before complete remission is achieved, and relapse is defined as an event which occurs after complete remission has been achieved. Due to the fact that regression of lymphoma is often incomplete in LBL it is not useful to distinguish between disease progression and relapse. Disease progression or relapse are defined as follows:

- Bone marrow progression/relapse is diagnosed in cases of ≥ 25% lymphoblasts in the bone marrow. If disease progression has been diagnosed other than by biopsy, then the BM is considered to be involved if it contains ≥ 5% lymphoblasts.
- CNS progression/relapse is diagnosed if lymphoma cells are present in the CSF and the cell count ≥ 5 µl and/or in cases of (re)appearance of an intra-cerebral tumor.

- Appearance of new manifestations
- Local manifestations: reappearance or increase in size of residuals
- Testes: increase in volume

Non-response, progression or relapse in patients with B-NHL/B-AL

Non-response in the CNS is diagnosed in cases of persistence of CSF blasts during the third course. Bone marrow non-response is defined as persistent blasts prior to the third course. Like in LBL, it is progressive disease or relapse are not individually distinguished. Both are defined as follows:

- Appearance of new manifestations or increase in size of known manifestations by more than 25%.
- Bone marrow progression/relapse is diagnosed in cases of ≥ 25% blasts in the bone marrow. If disease progression has been diagnosed other than by biopsy, then the BM is considered to be involved.
- CNS progression/relapse is diagnosed if blasts become detectable during treatment of CSF negative patients or if the blast count in the CSF increases significantly in CNS positive patients, or in cases of (re)appearance of an intra-cerebral tumor.

Non-response, progression or relapse in patients with ALCL

In ALCL non-response, progressive disease or relapse are not individually distinguished. This event is defined as follows:

- Appearance of new manifestations or increase in size of known manifestations by more than 25%.
- Bone marrow progression/relapse is diagnosed in cases of ≥ 25% blasts in the bone marrow. If disease progression has been diagnosed other than by biopsy, then the BM is considered involved if it contains ≥ 5% blasts.
- CNS progression/relapse is diagnose, if blasts become detectable during treatment in CSF negative patients or if the blast count in the CSF increases significantly in CNS positive patients, or in cases of (re)appearance of an intra-cerebral tumor.

Secondary malignancies

Any malignancy which is diagnosed during or after the treatment of NHL is regarded as a secondary malignancy. In cases of acute lymphoblastic leukemia, Hodgkin lymphoma or Non-Hodgkin lymphoma as secondary malignancies, molecular genetic analyses may be indicated to exclude a clonal relation between both manifestations.

Death due to any cause

Death due to any cause, regardless of the cause, i.e., related to the disease or not, is regarded as an event.

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5. APPENDICES A, B, C, D: THERAPEUTIC STRATEGIES FOR LBL, ALCL, AND MATURE B-NHL AND B-AL