Childhood ALL 1st relapse guidance

- ALL-IC study group, 2016 -

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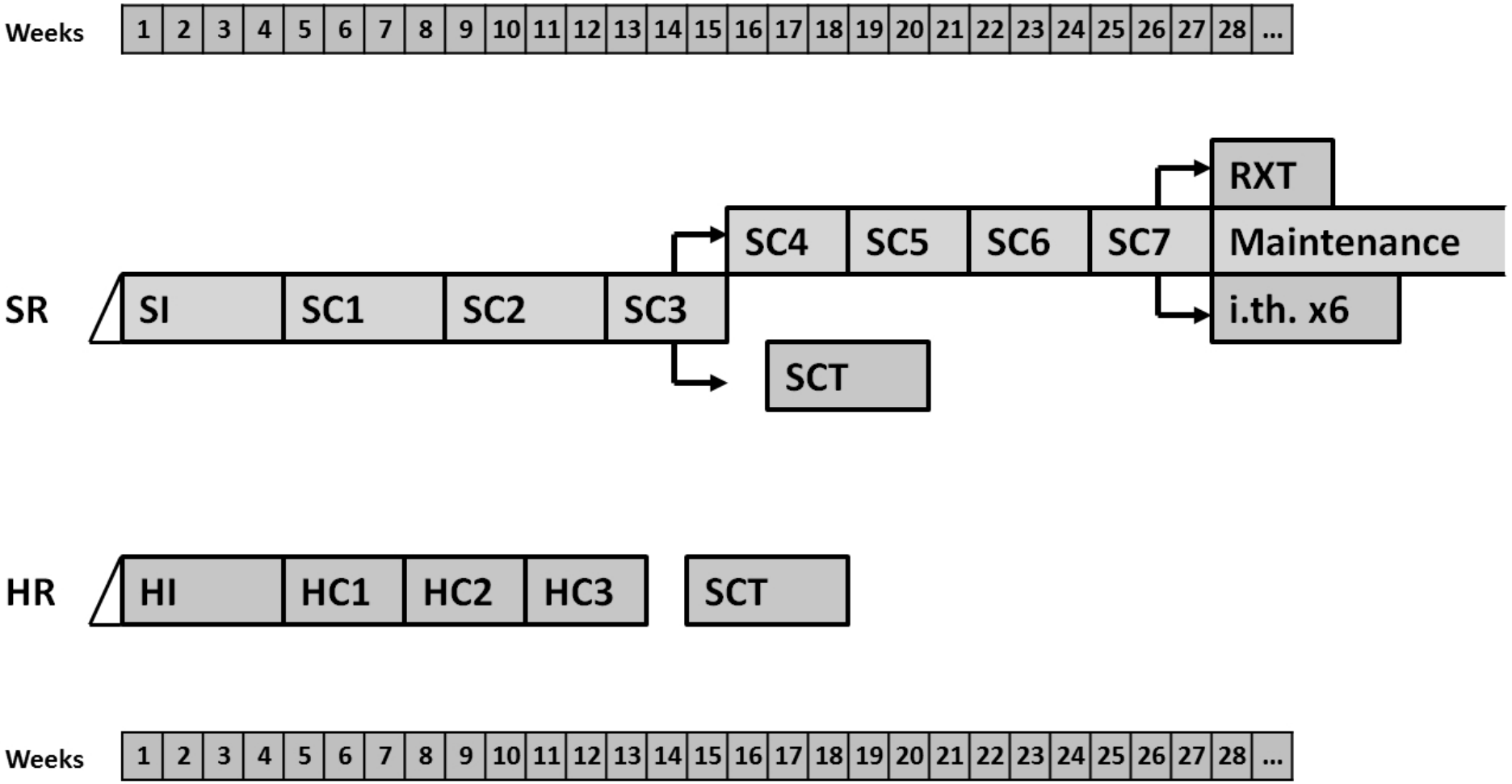
ALL 1st relapse guidance, ALL-IC study group, 2016



SYNOPSIS

Title	**Childhood ALL 1st relapse guidance, ALL-IC study group, 2016 "ALL-IC REL 2016"**
Steering committee	Janez Jazbec, Slovenia - chair Dániel Erdélyi, Hungary Juan Tordecilla, Chile Monica Makiya, Argentine Sophia Polychronopoulou, Greece Volkan Hazar, Turkey
Background	The Acute Lymphoblastic Leukemia Inter Continental (ALL-IC) Study Group is nearing completion of its second frontline ALL trial. By standardizing therapy and involving flow cytometry based MRD in treatment stratification, patient outcomes greatly improved. Still 15-20% of patients relapse, and their survival lags behind that achievable according to results of best published studies.
Objective	• To improve the outcome of ALL 1st relapse in children • To set up an international treatment platform with homogenized treatment approach among the ALL-IC community • To prepare the way for future clinical studies within the ALL-IC study group
Design	This is not a formal clinical trial, but a "current best practice guidance" optimized for the resources available in the ALL-IC countries at present. No randomization or new drugs are involved.
Risk group stratification	Patients are grouped for standard and high risk chemotherapy regimens and according to eligibility for stem cell transplantation (SCT). Criteria for high risk group: (1) any T-cell relapse involving the bone marrow (BM), (2) any very early relapse, (3) any early isolated BM relapse, (4) all relapses after SCT, (5) certain genetic subgroups. All others are stratified as standard risk. Eligibility for SCT: All high risk patients; standard risk patients with poor initial treatment response defined as bone marrow MRD ≥ 0.1% by flow cytometry on day 29. Certain genetic subgroups will also be eligible for SCT.
Inclusion and exclusion criteria	Inclusion criteria: • Confirmed morphologic diagnosis of 1st relapse of precursor lymphoblastic leukemia • Age 0-18 years at the time of relapse • Written informed consent • The participating center has access to flow cytometry MRD measurement as per standards of the ALL IC study group Exclusion criteria: • Mature B-ALL • Pregnant or breast feeding patient

LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
ALL-IC	The Acute Lymphoblastic Leukemia Intercontinental Study Group
BFM	Berlin-Frankfurt-Münster Study Group
AML1	Acute myeloid leukemia 1 (gene)
ARA-C	Cytarabine
BCP	B-cell precursor
BM	Bone marrow
BSA	Body surface area
CAR	Chimeric antigen receptor
CNS	Central nervous system
CR	Complete remission
CSF	Cerebrospinal fluid
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMSO	Dimethylsulfoxide
DI	Delayed intensification
EM	Extramedullary
F1-2	ALL Rez BFM 2002 protocol "F" cycles
FAB	French-American-British morphological classification
GI	Gastrointestinal
GR	Good response
HC	High-risk arm consolidation
HD	High-dose
HI	High-risk arm induction
HLA	Human leucocyte antigen
HR	High risk
iAMP21	Intrachromosomal amplification of chromosome 21
IEM	Isolated extramedullary
IntReALL	International Study for Treatment of Childhood Relapsed ALL
IT	Intrathecal treatment
IV	Intraveneous treatment
M0-3	Cytological bone marrow status 0-3
MD	HLA matched donor
MMD	HLA Mismatched donor
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NT5C2	5'-nucleotidase, cytosolic II (gene)
PBX1	PBX homeobox 1 (gene)
PEG	Polyethylene glycol
PCR	Polymerase chain reaction
PR	Poor response
RBC	Red blood cell count
R blocks	ALL relapse chemotherapy courses of the BFM group
REL	Relapse
SCT	Stem-cell transplantation
SC	Standard risk arm consolidation
SI	Standard risk arm remission induction

SR	Standard risk
TCF3	Transcription factor 3 (gene, alias of E2A)
TCR	T-cell receptor
TP53	Tumour protein p53 (gene)
TKI	Tyrosine kinase inhibitor
WBC	White blood cell count

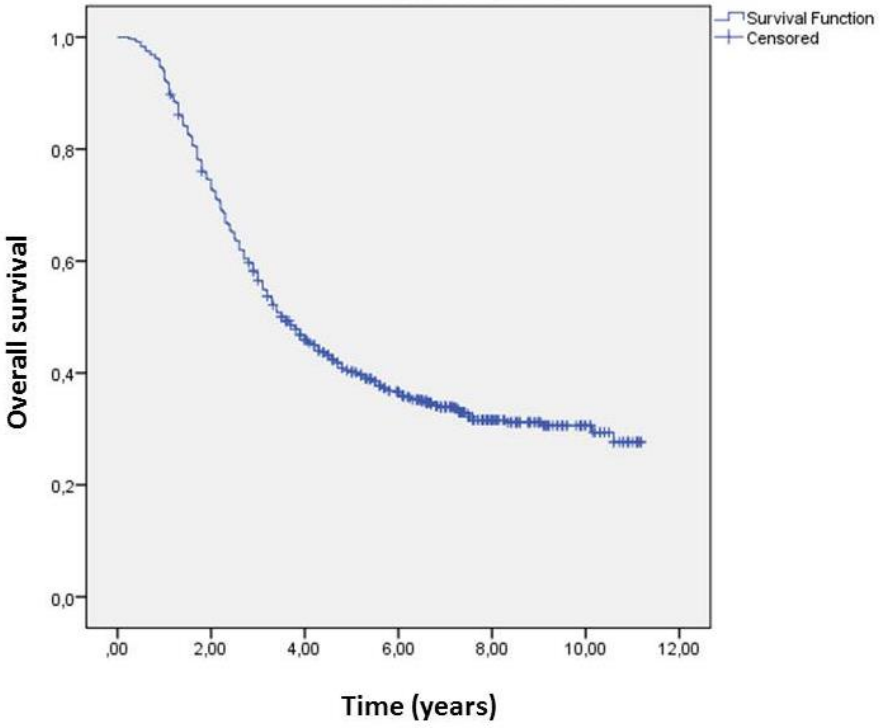
INTRODUCTION

From 2002 to 2007, the International Berlin-Frankfurt-Münster Study Group conducted a prospective randomized clinical trial (ALL IC-BFM 2002) for the management of childhood acute lymphoblastic leukemia (ALL) in 15 countries on three continents. The aim of this trial was to explore the impact of differential delayed intensification (DI) on outcome in all risk groups. For this trial, 5060 eligible patients were divided into three risk groups according to age, WBC, early treatment response, and unfavorable genetic aberrations. At 5 years, the probabilities of event-free survival and survival were 74% and 82% for all 5060 eligible patients, 81% and 90% for the SR (n=1564), 75% and 83% for the IR (N=2650), and 55% and 62% for the HR (N=846) groups, respectively. The ALL IC-BFM 2002 trial is a good example of international collaboration in pediatric oncology. A wide platform of countries able to run randomized studies in ALL has been established. Although the alternative DI did not improve outcome compared with standard treatment and the overall results are worse than those achieved by longer established leukemia groups, the national results have generally improved.

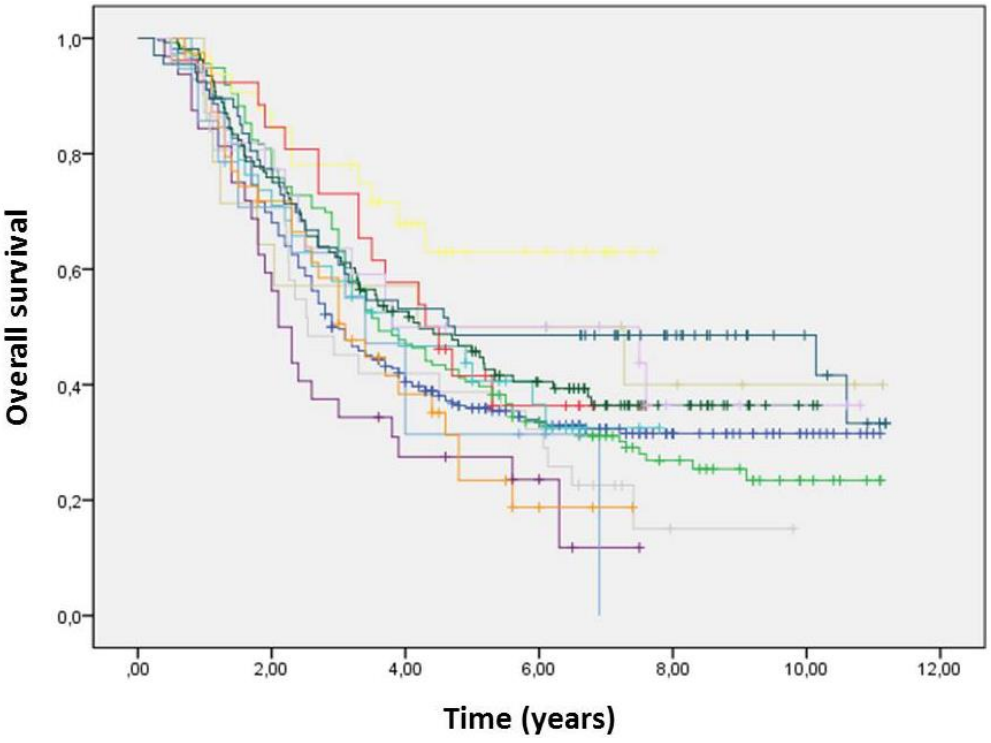
After the results of ALL IC 2002 study have been published, representatives of IC study groups have discussed the question of relapsed patients, during the IC-BFM meeting in Prague in 2014. Although the collection of data on patients who relapsed in ALL IC-BFM 2002 was not a part of the study, in 2013 all the participating centers were approached to collect the essential data of the patients who relapsed. The data on 834 patients were collected from 14 study groups. As relapse treatment was not part of the original study, the collected data were not complete and varied substantially among study groups. Nevertheless it was possible to conclude that more than 20 different treatment protocols were employed, while for 37% of patients there were no data on the treatment of relapse. The overall survival rate at 5 years was 40%, but varied significantly between the study groups (from 63% to 23%). It was noted that there have been extreme results on both sides, but also beside this extremes there was substantial variability among the remaining groups (Figures 1. and 2.). Based on this the IC BFM group concluded that relapsed patients would benefit from more standardized approach, which would include diagnostic and stratification criteria as well as standardized treatment recommendations.

The members of ALL-IC SG were in agreement that current IntReALL 2010 protocol design may be currently unfeasible for the majority of the ALL-IC SG countries. Although some of them may be able to join the core BFM group in the study of ALL relapse, most of them are currently not able to participate. The aim of the proposed strategy is to develop best practice guidance for ALL-IC countries, an observational study for the treatment of children with relapsed ALL. This would employ the combination of drugs that are already available, without randomization in the first stage. The study group will establish a registry for relapsed ALL patients and evaluate results. The ultimate goal at this stage is to homogenize the diagnostic criteria and the treatment in a way that would render the prospective acquisition of the data on the treatment of the children with relapsed ALL treated in the frame of ALL-IC countries possible. If this strategy turns out to be successful, this may serve as a platform for further studies which may tackle scientific questions in a randomized fashion.

1. Figure Overall survival of 834 ALL patients who were treated in ALL IC-BFM 2002 trial and relapsed.



2. Figure: Overall survival of 843 patients who relapsed on ALL IC-BFM 2002 trial, stratified by national study groups



We accept the IntReALL 2010 SR and HR study standard arms as best available practice for ALL-IC countries. The study group decided to apply their patient stratification and treatment prescriptions. This choice also makes it possible to cooperate with the IntReALL study group. In case IntReALL needs more patients to answer selected questions and certain ALL-IC centers are willing and able to join their investigations, using the same therapy backbone makes it possible to add IntReALL study drugs in randomized manner. Leaders of the IntReALL study group kindly provided our steering committee with their full study descriptions and gave permission for us to use its text. The patient stratification system, the treatment elements and many further parts of this document are extracts and adaptations of their study protocol.

As flow-cytometric determination of minimal residual disease was already an integral part of ALL-IC 2002 and 2009 studies and is a technology available for vast majority of ALL-IC countries, it is proposed to use flow-cytometry for estimation of minimal residual disease at the end of the fourth week of induction in the SR arm (after F2 block). A threshold of 0.1% will define suboptimal response as per the results of the ALL REZ BFM 2002 trial. Patients with poor response in the SR group will be candidates for allogenic bone marrow transplantation (SCT).

The ALL-IC SG is considering the options to establish a registry for their relapsed ALL cases. This may take longer time to organize. This guidance can be used regardless, with or without using the future registry, on the discretion of treatment centers within or outside of the ALL-IC SG.

Since this document is not a description of a clinical study but of a current best standard practice guidance, centers can implement any novel extensions or alterations depending on local possibilities. E.g. asparaginase enzyme activity monitoring and consequent changes of asparaginase therapy, or addition of new biological treatments are not discouraged within legal limits. However, the aim of the study group is to carry out these changes in a uniform and standardized way as much as possible within the study group. We can then monitor their efficacy and toxicity. Accordingly, we provided some recommendation on the use of some new agents (TKIs and nelarabine).

List of ALL-IC study groups planning to implement this guidance:

Argentina (GATLA)
Bulgaria
Chile
Croatia
Georgia
Greece
Hungary
Serbia
Slovenia
Turkey
Uruguay

OBJECTIVES

Main goals of the study are

- to set up a large international platform allowing for optimization of standard treatment strategies;
- to improve the outcome of children and adolescents with first relapsed acute lymphoblastic leukemia;
- to prepare the way for future clinical studies within the ALL-IC community on ALL relapse.

PROTOCOL DESIGN AND DESCRIPTION

Design

This is not a research study, but current best practice guidance optimized for the present resources available at the ALL-IC countries. It is designed as prospective open label international multi-center two arm observational study, without randomization.

Inclusion criteria:

- Confirmed morphologic diagnosis for 1st relapse of precursor lymphoblastic leukemia
- Age 0-18 years at the time of relapse
- Written informed consent
- The participating center has access to flow cytometry MRD measurement as per standards of the ALL IC-BFM 2009 study.

Exclusion criteria:

- Mature B-ALL
- Pregnant patient
- Lactation

During the course of treatment, individual patients are excluded in case of one of the following situations:

- Withdrawal of consent
- Pregnancy
- Retroactive failure to fulfill inclusion/exclusion criteria
- Significant non-compliance
- New medical conditions not allowing for continuation of the protocol conform treatment

Patients excluded from the study are further observed and considered for intention to treat analyses unless they withdraw their consent for registration within the study.

Requirements for centers

Requirements for treatment centers applying this guidance:

- A physician fully trained in pediatric hematology/oncology should direct the treatment at the site;
- Access to hematologic laboratory facilities for cytological diagnosis;
- Flow cytometry lab certified by ALL-IC standards;
- Access to radiotherapy facilities;
- Access to intensive care;
- Fulfilling the national criteria for pediatric hematology/oncology centers.

Treatment strategy

Fundamentally, this guidance adapts the strategies of standard (non-investigational) arms of IntReALL trials to ALL-IC countries. No experimental drugs will be used. The main deviation from IntReALL is that MRD will be measured by flow cytometry instead of the PCR based approach at IntReALL. When establishing the indication of SCT in the SR group, the same MRD time point and cut off will be used as that found effective in the intermediate arm of the ALL REZ BFM 2002 trial, by PCR. Various study groups found that MRD by flow cytometry and MRD by IgH or TCR based PCR correlate very well in general, as well as in the specific situation of childhood ALL relapse end-of-induction time point.

Apart from the differences above, patient stratification, systemic chemotherapy and local disease control strategies of the IntReALL trials will be applied.

DEFINITIONS AND PATIENT STRATIFICATION

Prognostic factors within the relapsed cohort

The time-point of relapse is defined in relation to the date of primary diagnosis and the date of completion of primary therapy. Completion of primary therapy is defined as the end of the anti-leukemic therapy of the frontline protocol. This is in most cases the end of the maintenance therapy, but may also be the last treatment after interruption of the intensive treatment, or of an inadequately short primary therapy. Since the duration of maintenance therapy varies between different protocols and individual patients (in most patients and protocols total treatment duration of 24 months), completion of primary therapy is a flexible time point in contrast to time point definitions referring to the date of primary diagnosis. Data from the ALL REZ BFM Study Group clearly show that the end of frontline therapy is more important for the prognosis than the absolute duration of 1st CR (unpublished). "Good risk" i.e. late relapses can be withheld by a prolongation of maintenance therapy, and ALL relapses have a good prognosis if they occur more than 6 months after the end of an inadequately short primary therapy.

The site of relapse is determined on the basis of conventional light microscopy using the FAB criteria. In morphologically unclear situations such as bone marrow involvement of extra medullary relapse around 5%, minimal residual disease quantification may be regarded as secondary criteria to determine the extent of bone marrow involvement.

1. Table: Categories for time to relapse

Time	**After initial diagnosis**		**After completion of initial treatment**
Late			≥ 6 months
Early	≥ 18 months	and	< 6 months
Very early	< 18 months	and	< 6 months

2. Table: Definition of sites of relapse

		Bone marrow involvement		
		<5% blasts	**5-25% blasts**	**≥25% blasts**
Extramedullar involvement	**no**	No relapse	Requires monitoring	Isolated bone marrow relapse
	yes	Isolated extramedullar relapse	Combined relapse	

Risk stratification

High Risk Group:

- Most patients will be categorized as high risk based on immunophenotype, site and time of relapse, as per 3. Table.
- All relapses that occur after SCT regardless of other risk factors,
- Patients with certain genetic abnormalities may also be stratified as HR, independently from other risk factors. See the recommendations of the I-BFM Resistant Disease Working Group at Appendix 2 in page 43. The available diagnostic tools vary among ALL-IC countries. Implementation of genetic stratifying factors is encouraged but not compulsory.

Standard Risk Group: those not stratified as high risk.

3. Table: Definitions of risk groups based on immunophenotype, site and time of relapse

	Non-T immunophenotype			T immunophenotype		
	Isolated extramedullar	Combined	Isolated marrow	Isolated extramedullar	Combined	Isolated marrow
Very early	HR	HR	HR	HR	HR	HR
Early	SR see Table 4	SR	HR	SR see Table 4	HR	HR
Late	SR	SR	SR	SR	HR	HR

The immunophenotype is defined according to EGIL criteria

Indication for allogeneic stem cell transplantation

The SCT procedure is not part of this protocol. It is recommended to include patients with SCT indication into the national SCT studies and protocols as far as available to warrant a quality controlled and homogeneous treatment.

Regarding the SR group, patients are eligible for allogeneic SCT if bone marrow MRD quantified by flow cytometry after induction is $\geq 10^{-3}$. Depending on the available donor, SCT indications are further refined in Table 4. If MRD cannot be quantified after induction at all, patients with late BM relapse are eligible for MD-SCT but not for MMD-SCT and patients with early combined BM relapse are eligible for both MD and MMD-SCT. For the patients in whom SCT is not possible, treatment with eight R blocks (R1 interchangeably with R2) is planned with cranial or craniospinal irradiation and 24 months of maintenance therapy.

SCT is planned for all the patients in HR group.

4. Table: Indication for allogeneic stem cell transplantation in the SR arm, following the IntReALL 2010 protocol

SCT	SR							
	Late isolated or combined BM relapse			Early combined BM relapse			Isolated EM relapse	
	MRD GR	MRD PR	MRD ND	MRD GR	MRD PR	MRD ND	Late	Early
MD*	No	Yes	Yes	Yes	Yes	Yes	No	Yes
MMD**	No	Yes	No	No	Yes	Yes	No	No

* Matched donor is defined as at least 9 out of 10 HLA allele identical with high-resolution typing of HLA A, B, C, and DQ, DR. ** Mismatched donor is defined as less than 9 out of 10 HLA allele identical (= more than 1 antigen mismatch). Abbreviations: BM, bone marrow; GR, good response as defined by the specific SR-arm; HR, high risk; EM, extramedullary; MD, matched donor; MMD, mismatched donor; MRD, minimal residual disease after induction; ND, not done; PR, poor response, as defined by the specific SR arm; SCT, stem-cell transplantation; SR, standard risk.

If SCT is not possible in a HR patient due to any reason, the outlook is very poor. This situation may arise either for the patient not reaching remission after cycle No. 3, or lack of donors or severe toxicities hindering SCT. We leave the decision of further treatment to the responsible physician, who may consider switching to experimental treatments (CAR T-cells, blinatumomab or Phase I or II studies if available), or administering further chemotherapy or changing to palliative treatment.

Deviations from guidance

In addition to those mentioned above, there may be biological subgroups of patients who benefit from SCT. The decision on SCT in this quickly changing and developing field should be made on the individual basis by the treating physician, based on the available set of tests at the given center. We encourage seeking for expert advice.

On the other hand only evidence based deviations are encouraged. For example availability of a matched sibling donor on its own should not justify SCT in childhood relapsed ALL with otherwise good prognostic factors.

Definitions on treatment response

The assessment of the response to therapy in bone marrow and CSF is based on cytologic criteria.

Complete Remission (CR)
Remission bone marrow **(M1)** and no further evidence of persistent leukemic lymphoblasts based on cytological histopathologic, radiologic or clinical findings. Absence of extramedullary leukemic involvement.

Aplastic bone marrow (M0)
Representative bone marrow aspirate with only few nucleated cells (mostly lymphocytes, cellularity resembles normal blood count in cytological analysis) without signs of regenerating normal hematopoiesis and with residual leukemic cells < 5%.

Complete bone marrow remission (M1)
Representative bone marrow aspirate with less than 5% lymphoblasts, satisfactory cellularity and signs of regenerating normal hematopoiesis

Partial response / marrow involvement (M2)
Bone marrow with ≥ 5% and < 25% of lymphoblastic cells irrespective of the cellular content.

Metaplastic marrow (M3)
Bone marrow with ≥ 25% of lymphoblastic cells irrespective of the cellular content.

Non-representative bone marrow
Markedly reduced cellularity despite signs of regeneration in the peripheral blood and differential count of nucleated cells in the marrow largely corresponding to that in the peripheral blood. Such a bone marrow aspirate should be repeated, particularly when therapeutic decisions are taken based on the result.

MRD reappearance
A reconversion after MRD negativity to reproducible MRD positivity (at least one sample, collected during post-consolidation) is called MRD reappearance. A reconfirmation is strongly recommended. This finding does not fulfil the conditions for the definition of subsequent relapse.

Subsequent relapse (REL)
A subsequent relapse is defined as evidence of ALL after achievement of 2nd CR as defined for the first ALL relapse.

DIAGNOSTICS

The diagnostic procedures before start of the study treatment (day 1 of week 1) are not part of the study. They are essential to establish the correct diagnosis as prerequisite for assessment of the in- and exclusion criteria.

Bone marrow relapse

Bone-marrow involvement is assessed by light microscopy applying the French-American-British (FAB) criteria. If the aspiration is insufficient (sicca), a bone marrow biopsy should be taken instead and referred to pathology. In this case, the aspiration is repeated after a few days of dexamethasone prephase, which usually leads to mobilization of the blast cells. If the extent of bone marrow involvement quantified by cytomorphology is inconclusive, MRD techniques may be considered in addition.

CNS relapse

A CNS relapse is diagnosed if morphologically unequivocal leukemic lymphoblasts are detected in the CSF and there is a pleocytosis of >5/µL nucleated cells. If the CSF is contaminated with blood the following procedure is recommended after discussion with the national study center: If blasts are present in the CSF and the peripheral blood shows no blasts, a CNS relapse is assumed. If the proportion of blasts in the CSF is equivalent to the proportion of blasts in the peripheral blood the Steinherz/Bleyer algorithm is applied: if the ratio of WBC/RBC in the CSF exceeds the same ratio in the peripheral blood for > 2 times, a CNS involvement is assumed, otherwise a contamination is assumed. In unclear situations a case-by-case decision may be necessary. If blasts are present the patient receives the intensified intrathecal chemotherapy similarly to patients with CNS involvement but no cranial irradiation. If clinical signs of CNS involvement are present such as visual disturbances, polyphagia, cranial nerve palsies in the absence of CSF pleocytosis, the presence of a CNS relapse has to be confirmed or ruled out with all available diagnostic methods (cranial CT, MRI). If evidence of meningeal infiltration is found by imaging, a biopsy may have to be performed.

Testicular relapse

A testicular relapse is diagnosed in case of a uni- or bilateral painless testicular enlargement with infiltration of leukemic lymphoblasts confirmed by biopsy. The extent of enlargement has to be documented using an orchidometer. Ultrasound may help to detect leukemic infiltration. In case of a clinically normal or inconclusive contralateral testis a subclinical involvement should be ruled out by biopsy.

Other extramedullary sites of relapse

Any site, organ or tissue may be infiltrated by leukemia. To detect clinically not overt organ involvement, an explorative ultrasound examination of the abdomen and the

lymph node regions has to be performed. Additionally other radiological measures such as MRI or CT may be necessary to determine organ involvement. Usually, no specific local treatment has to be applied since systemic chemotherapy is not impaired by blood barriers. However, bradytrophic sites such as the anterior chamber of the eye may be involved requiring specific diagnostics and local therapy. If a local leukemic infiltration seems to be persistent during induction and early consolidation, a biopsy should rule out persistence of vital leukemic cells, otherwise, a local irradiation would be recommendable. This may be in particular an issue in case of mediastinal tumor of a T-ALL relapse and should be discussed individually with the national study center.

Leukemia specific diagnostics

The diagnosis of relapsed ALL relies on cytological, immunological, cytogenetic and molecular genetic investigations, ploidy assessment. A full set of tests should be used for optimal treatment stratification and comprehensive characterization of leukemia. On follow up at set time points, cytology and flow cytometry will be used on all bone marrow samples. Further tests can also be performed depending on cases and available markers in a personalized approach, aiming for further improving or confirming MRD assessment.

Quantification of minimal residual disease

Minimal residual disease (MRD) is quantified by flow cytometry in bone marrow taken at defined time points during treatment of all patients.

Planned time points for bone marrow aspiration and MRD at Standard arm:

- SI day 15 - optional
- SI day 29 – compulsory
- Before SC2 – optional
- Before SC3 – compulsory
- During consolidation: after each cycle if previous sample was MRD positive
- Before SCT

Planned time points for bone marrow aspiration and MRD at High risk arm:

- HI day 29 – compulsory
- Before cycles SC2 and SC3 –only if the previous sample was MRD positive, otherwise optional
- Before SCT – compulsory

General medical diagnostics

At diagnosis, a complete work up of infection parameters and organ function is performed as basic values for further monitoring. This includes biochemistry, coagulation parameters, virology, HLA-typing, ultrasound of abdomen, testes, lymph nodes and venous vessels for central line implantation, echocardiogram, chest X-ray.

TREATMENT

General recommendations on chemotherapy

Dose reduction

Dose reductions may be applied as a definite exception in case of unacceptable toxicity or substantial treatment delays due to impaired tolerance to treatment. The need for dose reduction should be carefully reassessed prior to every treatment element. In general, one or several cytotoxic drugs may be reduced to 2/3 of the scheduled protocol dosage. In case of severe methotrexate associated toxicity such as mucositis, renal insufficiency and elimination failure, high-dose methotrexate may be given at a shorter infusion duration of 24 hours, at a lower dose of 500 mg/m^2, or with earlier given leucovorin rescue, eventually at higher (doubled) doses.

Full dose HR-arm chemotherapy can be attempted for patients relapsing at least half a year after SCT. If curative treatment is intended for earlier post-transplant relapses, reduction of treatment intensity is recommend on individual basis.

Body weight below 10 kg
In the rare case of a body weight below 10 kg at relapse, the drug doses are calculated according to body weight instead of body surface according to the following formula:
Dose = Scheduled dose for BSA [m^2] x body weight [kg] / 30

Obesity
For obese patients no general recommendations for dose reduction are made. In individual patients, dose adaptations may be made due to toxicity according to the recommendations made.

Down syndrome patients
Patients with Down syndrome and ALL-relapse have a worse tolerance to treatment as others and in particular a high induction death rate and mortality rate in CR2. Since the tolerance to HD methotrexate is in particular poor, the first application should be given at an infusion duration of 24 hours only and eventually at a reduced dose of 500 mg/m^2. Only if this schedule is well tolerated, the next HD MTX may be adjusted to the ways as scheduled in the protocol. For all other drugs, no general reduction of the doses is recommended. The option of dose reduction should be however applied in patients with Down syndrome more generously than in other patients.

Treatment intensity

The analysis of preceding studies suggests that treatment intensity is an essential parameter for the success of relapse therapy. Consequently, a prolongation of treatment-free intervals, particularly during the first two cycles must only be accepted in case of life threatening complications. The rather low blood count entry criteria to start the consequent cycle were not only set to prevent early initiation of the next block. Avoid or minimize delays beyond the set breaks among cycles, as much as starting laboratory criteria allow.

If previous experience with individual patients suggests, that a timely delivery of therapy is unlikely or associated with an undue risk because of intolerance, the protocol stipulates the possibility of dose reduction.

Furthermore, treatment may need to be postponed to allow the patient to recover from severe toxicity. The need to delay therapy has to be reassessed at least every other day. Thus, the treating physician should not blindly follow the protocol, but take into account the individual treatment tolerance of his patients and adapt the protocol to individual requirements, if necessary. In these cases we suggest to contact the national study coordinator.

Standard risk group

Patients in the SR group receive induction, consolidation and maintenance therapy according to a modified protocol ALL-REZ BFM 2002 with consolidation including the previous Protocol II-IDA cycle as 1st consolidation element. Induction consists of the optional prephase, a combined cycle as per previous blocks F1 and F2. At day 29 the cytological remission and the MRD status are quantified. Patients with MRD$\geq 10^{-3}$ (at least 1 leukemic cell out of 1000 mononuclear cells) at week 5 are allocated to allogeneic stem-cell transplantation (SCT) after the SC3 course, whereas the other patients continue with the study protocol followed by a maintenance therapy of 24 months duration and a total treatment duration of 131 weeks. At the beginning of maintenance therapy, all patients without CNS involvement receive triple intrathecal therapy once every 4 weeks for a total of 6 times, and are not subject to cranial radiotherapy. Patients with CNS involvement receive cranial irradiation at a dose of 18 Gray (Gy) and no intrathecal therapy during maintenance treatment. Boys with testicular relapse receive local treatment as described under the chapter "Local therapy" starting at page 34.

SI BLOCK

(Standard risk arm remission induction, ALL Rez BFM 2002 trial F1 and F2 cycles)

Agent	Dosage	Application	Week 1	Week 2	Week 3	Week 4
Dexamethasone	20 mg/m²/d	PO				
Vincristine	1.5 mg/m²	IV				
Methotrexate	1 g/m²	IV 36 h				
Cytarabine	2x3 g/m²/d	IV 3 h				
PEG-Asp.	1000 U/m²	IM / IV 2 h				
Methotrexate	Age dep.	IT				
Cytarabine	Age dep.	IT				
Prednisolone	Age dep.	IT				
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

Criteria to start and guide the course
No specific blood counts or clinical conditions are mandatory to start week 1 and 3. In case of renal insufficiency (elevated creatinine) MTX 1g/m² should be avoided and induction should be started with week 3.

Diagnostic measures
Bone marrow aspirate at day 1 of week 3 is optional. Results might help to guide treatment in case of clinical complications. Bone marrow aspiration on day 29 is compulsory, it is of key importance for further treatment stratification. A non-representative marrow at this time point warrants repeated sampling and the start of the next cycle should be postponed accordingly. If aplastic (M0) marrow is gained, aspiration should be repeated within one week, depending on full blood count suggesting bone marrow recovery.

Dexamethasone
20 mg/m² (max. 40 mg/day) orally divided in two daily doses on day 1-5 of week 1 and 3. A dexamethasone **prephase** can be started from day -5 until day 0 at a dose of 6 mg/m² in case of high tumor burden or to bridge the time until start of the study.

Vincristine
1.5 mg/m² (maximum single dose 2 mg) as 15 min short infusion (or as IV bolus not on the same day as IT therapy) on day 1 and 6 of week 1 and on day 1 of week 3.

MHD IV Methotrexate
1 g/m² IV over 36 hours starting on day 1 of week 1. 10% is given as a 30 min bolus and the remaining 90% as a continuous infusion for 35.5 hours. Concomitant alkaline hydration with 3000 ml/m²/24 hours is given on day 1 and 2. Rescue with folinic acid of 15 mg/m² is given at 48 and 54 hours after start of MTX. Serum methotrexate levels can be measured at 36h and 48h after the start of the MTX infusion, and the dose of folinic acid adapted to elevated MTX serum levels. See further details at chapter "Impaired elimination of methotrexate" in page 39.

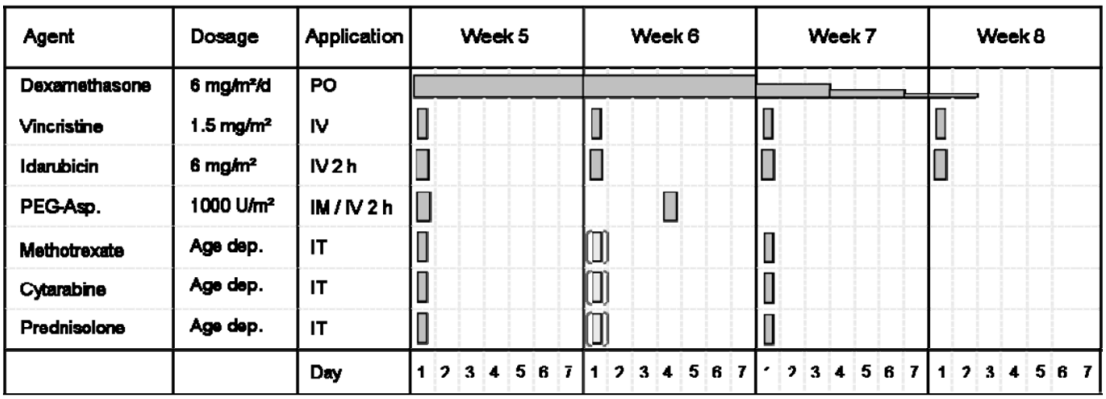
PEG-asparaginase
1000 units/m² as 2-hour infusion or intramuscularly on day 4 of week 1 and day 4 of week 3. The infusion of L-asparaginase should be started at a reduced rate and increased stepwise, if applicable. See further notes on alternative agents in chapter "Asparaginase preparations" in page 37.

Cytarabine
3 g/m² as 3 hour infusion every 12 hours on day 1 and 2 (a total of 4 doses) of week 3. A prophylaxis of conjunctivitis with eye drops and of neuropathy with vitamin B6 at a dose of 100 mg/m² IV is recommended prior to each cytarabine dose.

Intrathecal chemotherapy
Age adapted doses of methotrexate, cytarabine and prednisolone (see 5. Table in page 36) are administered on day 1 of week 1, and day 5 of week 3. This can be administered directly before or any time until the end of the methotrexate infusion. Patients with CNS involvement receive an additional intrathecal injection on day 6 of week 1 and weekly doses until two clear CSF samples are obtained.

SC1 BLOCK

(Standard risk arm, 1st cycle of consolidation, week 5-8)
(ALL Rez BFM 2002 trial, Protocol II IDA, phase 1)



Criteria to start and guide the course

Start of week 5 and application of vincristine / idarubicin at weeks 6-8 requires neutrophils > 0.5 x 10^9/L and a clinical status allowing for treatment continuation each time. Dexamethasone is given without discontinuation.

Diagnostic measures

Bone marrow aspirate at induction day 1 of week 5 is obligatory to assess cytological remission and MRD response. Results should reveal a representative marrow. In case of a non-representative or an aplastic marrow the analysis should be repeated and the start of therapy postponed accordingly. In case of persistent ALL with up to 25% leukemic cells in the BM, the treatment should be continued irrespectively of the cellularity.

Dexamethasone:

6 mg/m² orally divided in two daily doses on day 1-7 of week 5 and 6, tapering the dose to 3 mg/m² on day 1-3 of week 7, 1.5 mg/m² on day 4-6 of week 7, and 0.75 mg/m² on day 7 of week 7 and day 1-2 of week 8.

Vincristine

1.5 mg/m² (maximum single dose 2 mg) as 15 min short infusion (or as IV bolus not on the same day as IT therapy) on day 1 of week 5-8.

Idarubicin

6 mg/m² as infusion over 2 hours on day 1 of week 5-8.

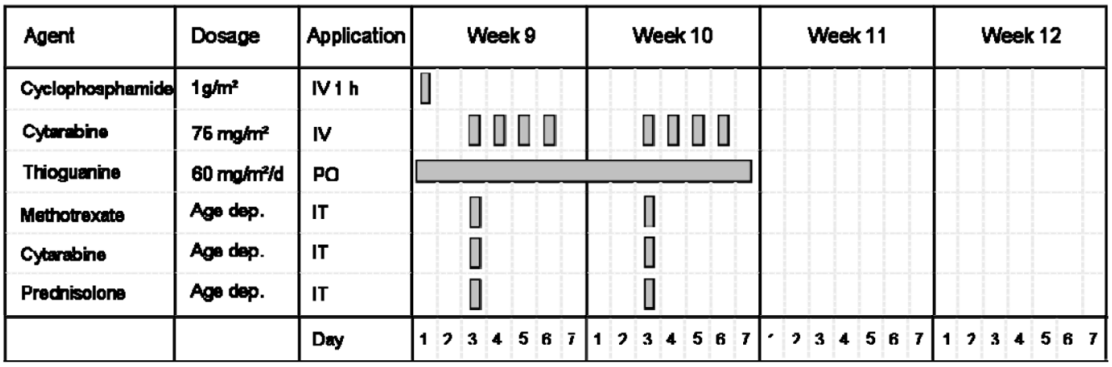
PEG-asparaginase

1000 units/m² as 2-hour infusion or intramuscularly on day 1 of week 5 and day 4 of week 6. The infusion of PEG-asparaginase is started at a reduced rate and increased stepwise, if applicable. See further notes on alternative agents under chapter "Asparaginase preparations" in page 37.

Intrathecal chemotherapy
Age adapted doses (see 5. Table in page 36) of methotrexate, cytarabine, and prednisolone are administered on day 1 of week 5 and 7. Patients with CNS involvement receive an additional triple intrathecal therapy on day 1 of week 6.

SC2 BLOCK

(SR arm, 2nd cycle of consolidation, week 9-10)
(ALL Rez BFM 2002 trial, Protocol II IDA, phase 2)



Criteria to start and guide the course
Start of week 9 requires leukocytes > 1.5 x 10^9/L, neutrophils > 0.5 x 10^9/L, platelets > 80 x 10^9/L, and a clinical status allowing for treatment continuation. Cytarabine courses on day 3 of weeks 9 and 10 are given irrespectively of the blood count as long as the clinical status allows for treatment continuation.

Diagnostic measures
Bone marrow aspirate at day 1 of week 9 is optional to assess cytological remission and MRD response. Results are not relevant for treatment stratification.

Cyclophosphamide
1 g/m² as 1-hour infusion on day 1 of week 9. Mesna is administered at a dose of 400 mg/m² IV prior to as well as 4 and 8 hours after the cyclophosphamide. Hydration with 3000 ml/m² is administered for 24 hours from start of cyclophosphamide.

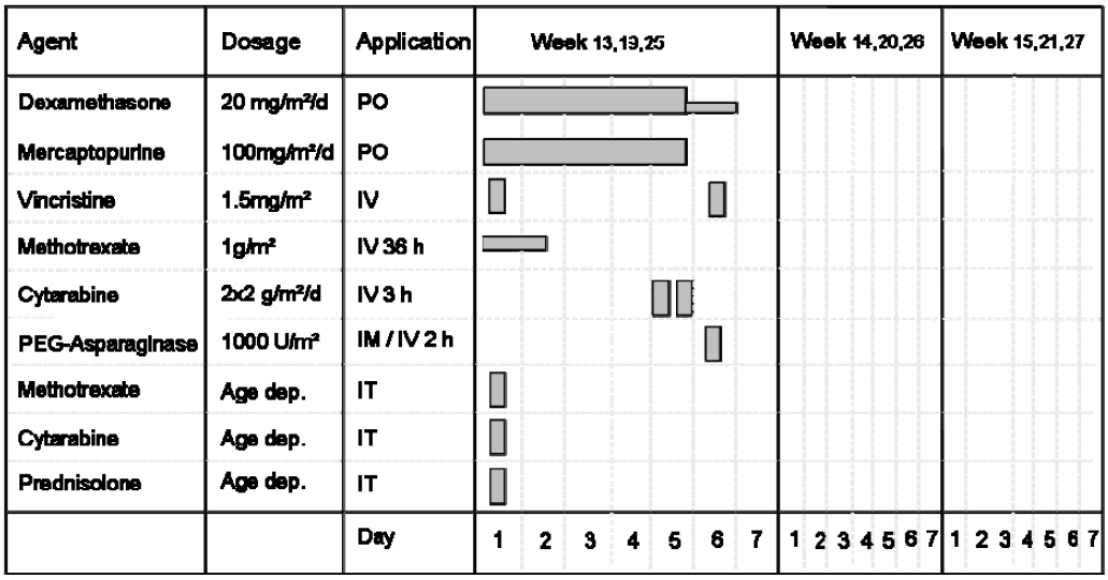
Cytarabine
75 mg/m² as IV bolus on day 3-6 of week 9 and 10.

Thioguanine
60 mg/m² orally on day 1-7 of week 9 and 10.

Intrathecal chemotherapy
Age adapted doses (see 5. Table in page 36) of methotrexate, cytarabine, and prednisolone are administered on day 3 of week 9 and 10.

SC3, SC5, SC7 BLOCKS

(SR arm, 3rd, 5th, 7th cycle of consolidation, weeks 13-15, 19-21, 25-27)
(ALL Rez BFM 2002 trial, R1 cycle)



Criteria to start and guide the course

Start of the course (week 13, 19, or 25) requires leukocytes > 2.0 x 10^9/L, neutrophils > 0.5 x 10^9/L, platelets > 80 x 10^9/L, and a clinical status allowing for treatment continuation. In case of prolonged treatment delays, dose reductions have to be considered according to those described at chapter "General recommendations on chemotherapy" in page 19. After the SC3 course, at week 17, allogeneic SCT is scheduled, if indicated.

Diagnostic measures

Bone marrow aspirate at day 1 of week 13 is obligatory to assess cytological remission and MRD response. Results are not relevant for treatment stratification.

Dexamethasone

20 mg/m² (maximum 40 mg/d) orally, divided in two daily doses on day 1-5, and 10 mg/m² on day 6 of these blocks.

6-Mercaptopurine

100 mg/m² orally on day 1-5 of these blocks.

Vincristine

1.5 mg/m² (maximum single dose 2 mg) as 15 min short infusion (or as IV bolus not on the same day as IT therapy) on day 1 and 6 of these blocks.

Methotrexate IV

1 g/m² IV over 36 hours starting on day 1 of each course. Out of the total, 10% is given as a 30 min bolus and the remaining 90% as a continuous infusion for 35.5 hours. Concomitant alkaline hydration with 3000 ml/m²/24 hours is given on day 1 and 2. Rescue with folinic acid of 15 mg/m² is given at 48 and 54 hours after start of MTX.

Serum methotrexate levels can be measured at 36h and 48h after the start of the MTX infusion, and the dose of folinic acid adapted to elevated MTX serum levels. The management is guided according to recommendations in chapter "Impaired elimination of methotrexate" in page 39.

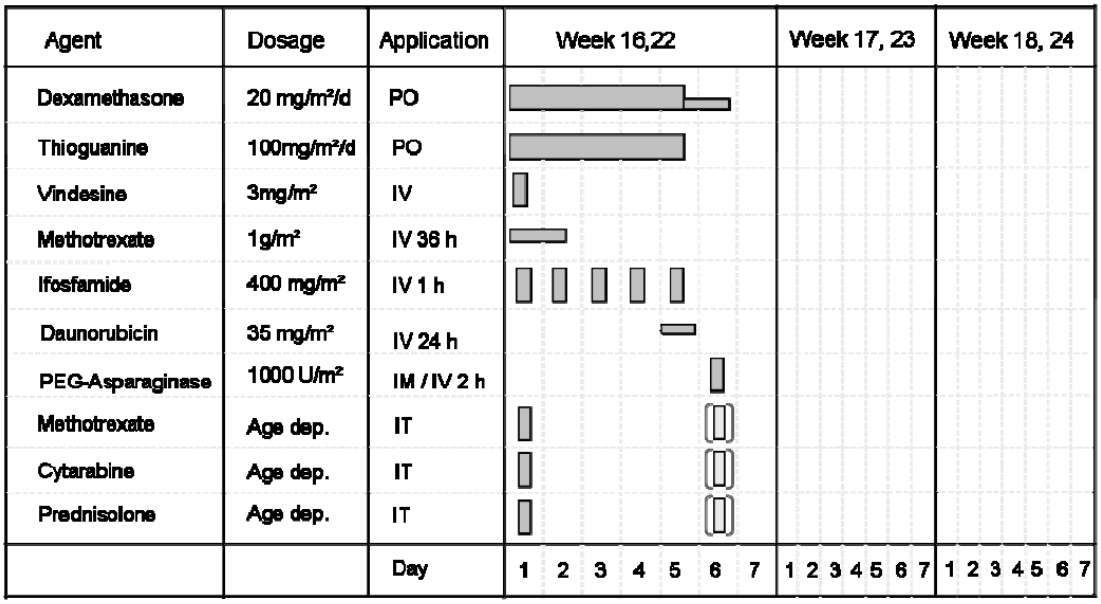
Cytarabine
2 g/m² as a 3-hours infusion every 12 hours on day 5 (a total of 2 doses) of SC3, SC5, SC7 cycles. A prophylaxis of conjunctivitis with eye drops and of neuropathy with vitamin B6 at a dose of 100mg/m² IV is recommended prior to each cytarabine dose.

PEG-asparaginase
1000 units/m² as 2-hour infusion or intramuscularly on day 6 of each of these cycles. The infusion of L-asparaginase should be started at a reduced rate and increased stepwise, if applicable. See further notes on alternative agents under chapter "Asparaginase preparations" in page 37.

Intrathecal chemotherapy
Age adapted doses (see 5. Table in page 36) of methotrexate, cytarabine, and prednisolone are administered on day 1 of each course directly before or during the methotrexate infusion.

SC4, SC6 BLOCKS

(SR arm, 4th, 6th cycle of consolidation, weeks 16-18, 22-24)
(ALL Rez BFM 2002 trial, R2 cycle)



Criteria to start and guide the course
Start of the course (week 16, or 22) requires leukocytes > 2.0 x 10^9/L, neutrophils > 0.5 x 10^9/L, platelets > 80 x 10^9/L, and a clinical status allowing for treatment continuation. In case of prolonged treatment delays, dose reductions according to the specific guidelines outlined in chapter "General recommendations on chemotherapy" in page 19 have to be considered.

Diagnostic measures
Bone marrow aspirate at day 1 of week 16 is obligatory to assess cytological remission and MRD response, if no allogeneic SCT is indicated or SCT is postponed. Results are not relevant for treatment stratification. Prior to courses SC 6 (week 22) no BM aspirate is foreseen. If allogeneic SCT is planned for week 17, BM aspirate is done in context with the SCT preparation and can be postponed accordingly.

Dexamethasone
20 mg/m² (maximum 40 mg/d) orally divided in two daily doses on day 1-5, and 10 mg/m² on day 6 of each SC4, or 6 course, week 16 and 22.

Thioguanine:
100 mg/m² orally on day 1-5 of each SC4 or 6 course, week 16 and 22.

Vindesine
3 mg/m² as 15 min short infusion (or as IV bolus not on the same day as IT therapy) on day 1 of each SC4 or 6 course, week 16 and 22.
In case vindesine is not available, it can be substituted with vincristine 1.5 mg/m² (maximum single dose 2 mg) as 15 min short infusion (or as IV bolus not on the same day as IT therapy).

Methotrexate IV
1 g/m² IV over 36 hours starting on day 1 of each SC4, or 6 course, week 16 and 22. 10% of the dose is given as a 30 min bolus and the remaining 90% as a continuous infusion for 35.5 hours. Concomitant alkaline hydration with 3000 ml/m²/24 hours is given on day 1 and 2. Rescue with folinic acid of 15 mg/m² is given at 48 and 54 hours after start of MTX. Serum methotrexate levels can be measured at 36h and 48h after the start of the MTX infusion, and the dose of folinic acid adapted to elevated MTX serum levels. The management is guided according to recommendations in chapter "Impaired elimination of methotrexate" in page 39.

Ifosfamide
400 mg/m² as a 1-hour infusion day 1-5 of each SC4 or 6 course, week 16 and 22. Mesna is administered at a dose of 200 mg/m² IV prior to as well as 4 and 8 hours after Ifosfamide. Hydration with 1500 ml/m²/day is administered from start of Ifosfamide until day 5.

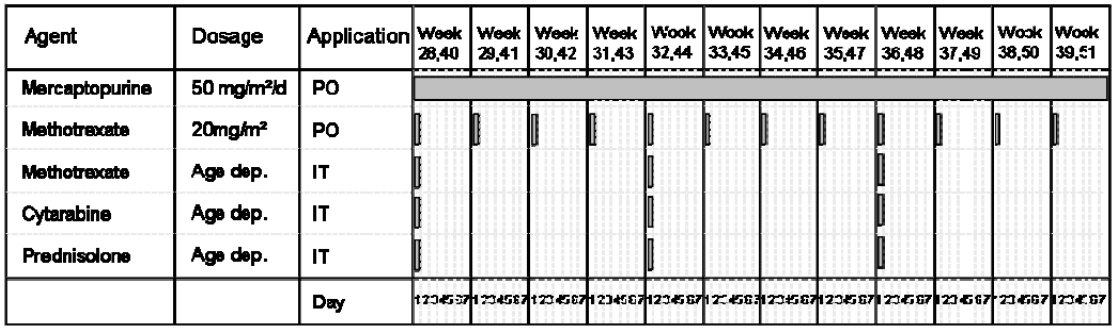
Daunorubicin
35 mg/m² as a 24-hour infusion on day 5 of each SC4 or 6 course, week 16 and 22.

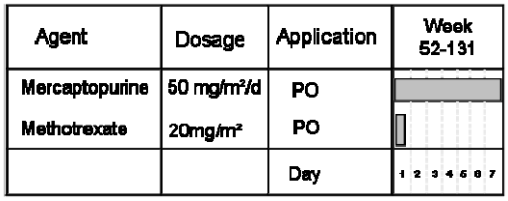
PEG-asparaginase
1000 units/m² as 2-hour infusion on day 6 of each SC4 or 6 course, week 16 and 22. The infusion of L-asparaginase should be started at a reduced rate and increased stepwise. See further notes on alternative agents under chapter "Asparaginase preparations" in page 37.

Intrathecal chemotherapy
Age adapted doses (see 5. Table in page 36) of methotrexate, cytarabine, and prednisolone are administered on day 1 of each SC4, 6 course, week 16 and 22, directly before or during the methotrexate infusion. Patients with CNS involvement receive an additional intrathecal injection on day 6 of each SCA4 or 6 course, week 16 and 22.

MAINTENANCE CHEMOTHERAPY

(SR arm, maintenance weeks 28– 131)





General structure
Maintenance therapy is given throughout from week 28 for a total of 104 weeks (= 2 years). During the first 24 weeks, a total of 6 applications of intrathecal chemotherapy are given only to those patients without prior CNS irradiation.

Criteria to start and guide the course
Start of maintenance (week 28) requires leukocytes > 2.0 x 10^9/L, neutrophils > 0.5 x 10^9/L, platelets > 80 x 10^9/L, and a clinical status allowing for treatment continuation. The dosing of mercaptopurine and methotrexate is adapted to the leukocyte count which should range between 2.0 and 3.0 x 10^9/L (150% of 6MP/MTX dose if WBC > 3.0 x 10^9/L, 100% if WBC >2.0 and < 3.0 x 10^9/L, 50% if WBC > 1.0 and < 2.0 x 10^9/L or if the lymphocyte count drops below 0.3 x 10^9/L, 0% if WBC < 1.0 x 10^9/L). Both drugs are started with reduced doses and weekly increased. In case of drop of leukocytes < 1.0 x 10^9/L, neutrophils < 0.5 x 10^9/L, and/or platelets < 80 x 10^9/L or in case of febrile episodes, the treatment is interrupted.

Diagnostic measures
Bone marrow aspirate at day 1 of week 28 at start of maintenance therapy and at the end of maintenance therapy (after week 131) are not obligatory and can be done at the discretion of the treating investigator to confirm cytological remission and continuous MRD response.

Mercaptopurine
50 mg/m² (adapted individually to leukocyte counts and toxicity) orally every day (day 1-7 of week 28 - 131). Doses should be taken at least one hour after the evening meal without milk products.

Methotrexate
20 mg/m² (adapted individually to leukocyte counts and toxicity) orally on day 1 of each week as a single dose.

Intrathecal chemotherapy
Age adapted doses (see 5. Table in page 36) of methotrexate, cytarabine, and prednisolone are administered on day 1 of week 28, 32, 36, 40, 44, 48 (6 application, every 4 weeks). Patients with CNS involvement and cranial irradiation at the start of maintenance therapy do not receive intrathecal therapy during maintenance therapy.

High risk group

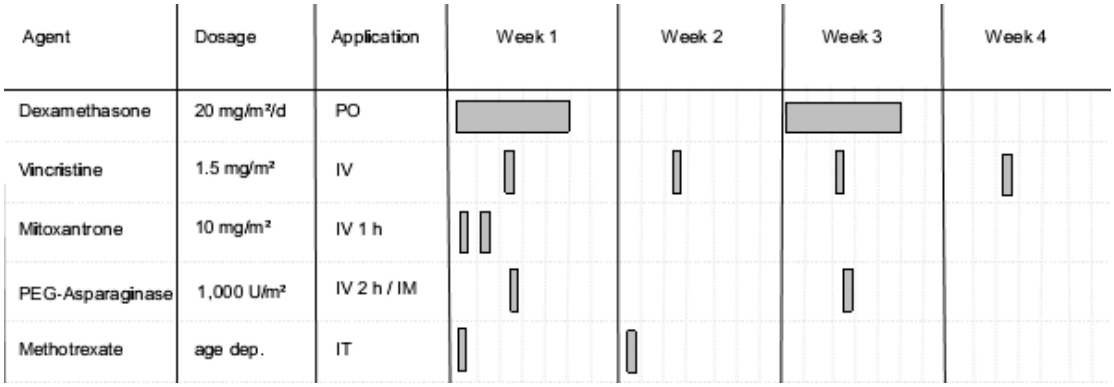
HR patients will receive induction with a modified ALL R3 protocol. At day 29 the cytological remission and the MRD status using flow-cytometry in the bone marrow are assessed. In case of M0, the bone marrow aspirate is repeated after 1 week.

Consolidation consists of an HC1 (modified ALL-AIEOP-BFM HR1) course at week 5 and an HC2 (modified ALL-AIEOP-BFM HR3) course at week 8. A third consolidation course HC3 (modified AIEOP-BFMHR2) scheduled at week 11 can be given within the protocol. Therapy delay or adjustments for medical reasons are not considered protocol violations. They should be documented in the patient's file.

Allogeneic SCT is performed after week 15. The procedure is not part of current protocol. In case of MRD persistence $\geq 10^{-3}$ at week 11, the national coordinating centers should be contacted for individual treatment recommendation. A general recommendation within the protocol is not given and a continuation of protocol conform therapy is well justified.

HI BLOCK

(High risk arm, Induction cycle, week 1-4)
(originally: R3 induction)



Dexamethasone
20 mg/m² (maximum 40 mg/d) orally divided into two daily doses on days 1-5 of weeks 1 and 3. A dexamethasone **prephase** can be started from day -5 until day 0 at a dose of 6 mg/m² in case of high tumor burden or to bridge the time until start of the study.

Vincristine
1.5 mg/m² (maximum single dose 2 mg) as 15 min short infusion or as IV bolus (not on the same day as IT therapy) on day 3 of weeks 1-4.

Mitoxantrone
10 mg/m^2 as 1-hour infusion on days 1 and 2 of week 1

PEG-asparaginase
1,000 units/m² as a 2-hour infusion or intramuscularly on day 3 of weeks 1 and 3. The infusion of asparaginase should be started at a reduced rate and increased stepwise, if applicable. See further notes on alternative asparaginase agents at chapter "Asparaginase preparations" in page 37.

Intrathecal chemotherapy
Age adapted dose (see table below) of methotrexate is administered on day 1 of weeks 1 and 2. Patients with CNS involvement receive additional intrathecal injections weekly thereafter, until two leukemia free CSF samples are obtained.

Age [years]	methotrexate [mg]	0.9% NaCl [ml]
< 1	6	1.5
1	8	2.0
2	10	2.5
≥ 3	12	3.0

HC1 BLOCK

(HR consolidation block 1, weeks 5-7)
(Modified ALL AIEOP-BFM HR1 course)

Agent	Dosage	Application	Week 5	Week 6	Week 7
Dexamethasone	10 mg/m²/d	PO			
Vincristine	1,5 mg/m²/d	IV			
ARA-C	2 g/m²	IV			
Methotrexate	1g/m²	IV 36 h			
Cyclophosphamide	200 mg/m²	IV 1 h			
PEG-Asparaginase	1000 U/m²	IV 2 h / IM			
Methotrexate	Age dep.	IT			
Cytarabine	Age dep.	IT			
Prednisolone	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

Criteria to start and guide the course

Start of the course requires granulocytes ≥ 0.5 x 10^9/L, thrombocytes ≥ 50x10^9/L and a clinical status allowing for treatment continuation. In case of prolonged treatment delays, dose reductions may be considered according to the specific guidelines outlined at chapter "General recommendations on chemotherapy" in page 19.

Diagnostic measures

Bone marrow aspirate on day 1 of week 5 is mandatory to assess cytological remission and MRD response. Results should reveal a representative marrow. In case of a non-representative or aplastic marrow, the analysis should be repeated and the start of next therapy postponed accordingly.

Dexamethasone

10 mg/m² orally divided into two daily doses on days 1-5 of week 5.

Vincristine

1.5 mg/m² (maximum single dose 2 mg) as 15 min short infusion or as IV bolus (not on the same day as IT therapy) on days 1 and 6 of week 5.

HD-Cytarabine

2 g/m^2/dose as a 3-hour infusion every 12 hours (total of 2 doses) on day 5 of week 5. Prophylaxis of conjunctivitis with eye drops every 6 hours during administration and of neuropathy with vitamin B6 at a dose of 100 mg/m^2 i.v. prior to each cytarabine dose is recommended.

Methotrexate IV

1 g/m^2 i.v. over 36 hours starting on day 1 of week 5. 10% is given as a 30 min bolus

and the remaining 90% as a continuous infusion over 35.5 hours. Concomitant alkaline hydration with 3000 ml/m^2/24 hours is given on day 1 and 2. Serum methotrexate levels can be measured at 36 hour and 48 hour after start of MTX infusion. Rescue with folinic acid at 15 mg/m^2 is given at 48 and 54 hours after start of MTX. The dose can be adapted to elevated MTX serum levels. See further details under the chapter "Impaired elimination of methotrexate" in page 39.

Cyclophosphamide
200 mg/m^2/dose as a 1-hour infusion every 12 hours on days 2-4 (total of 5 doses). Mesna is administered at 70 mg/m^2/dose before and at 4 and 8 hours after start of each cyclophosphamide infusion. Hydration with 3000 ml/m^2 is administered from start of cyclophosphamide until day 5.

PEG-asparaginase
1,000 units/m² as a 2-hour infusion or intramuscularly on day 6 of week 5. The infusion of asparaginase should be started at a reduced rate and increased stepwise, if applicable. See further notes on alternative asparaginase agents at chapter "Asparaginase preparations" in page 37.

Intrathecal chemotherapy
Age adapted doses (see 5. Table in page 36) of methotrexate, cytarabine and prednisolone are administered on day 2 of week 5. Patients with CNS involvement receive an additional intrathecal injection on day 7 of week 5.

HC2 BLOCK

(HR consolidation block 2 week 8-10)
(Modified ALL AIEOP-BFM HR3 course)

Agent	Dosage	Application	Week 8	Week 9	Week 10
Dexamethasone	10 mg/m²/d	PO			
ARA-C	2 g/m²	IV			
Etoposide	100 mg/m²	IV 1 h			
PEG-Asparaginase	1000 U/m²	IV 2 h / IM			
Methotrexate	Age dep.	IT			
Cytarabine	Age dep.	IT			
Prednisolone	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

Criteria to start and guide the course
Start of the course requires neutrophils ≥0.5 x 10^9/L, thrombocytes ≥50 x 10^9/L and a clinical status allowing for treatment continuation. In case of prolonged treatment delays, dose reductions may be considered according to the specific guidelines outlined at chapter "General recommendations on chemotherapy" in page 19.

Diagnostic measures
Bone marrow aspirate on day 1 of week 8 is optional. It is recommended to assess cytological remission and MRD response in patients who were MRD positive at the previous time point.

Dexamethasone
10 mg/m²/d (maximum 40 mg/d) orally divided into two daily doses on days 1-6 of week 8.

HD-Cytarabine
2 g/m^2/dose as a 3-hour infusion every 12 hours (total of 4 doses) on days 1-3 of week 8.

Prophylaxis of conjunctivitis with eye drops every 6 hours during administration and of neuropathy with vitamin B6 at a dose of 100 mg/m^2 i.v. prior to each cytarabine dose is recommended.

Etoposide
100 mg/m^2/dose as a 4-hour infusion every 12 hours on days 3-5 (total of 5 doses) of week 8. It should not be infused < 1 hour, since it can lead to hypotension.

PEG-asparaginase
1,000 units/m² as a 2-hour infusion or intramuscularly on day 6 of week 8. The infusion of asparaginase should be started at a reduced rate and increased stepwise, if applicable. See further notes on alternative asparaginase agents at chapter “Asparaginase preparations” in page 37.

Intrathecal chemotherapy
Age adapted doses (see 5. Table in page 36) of methotrexate, cytarabine, and prednisolone are administered on day 1 of week 8.

HC3 BLOCK

(HR consolidation course 3, week 11-13)
(Modified ALL AIEOP-BFM HR2 course)

Agent	Dosage	Application	Week 11	Week 12	Week 13
Dexamethasone	10 mg/m²/d	PO			
Vincristine	1,5 mg/m²/d	IV			
Daunorubicin	30 mg/m²	IV 24h			
Methotrexate	1g/m²	IV 36 h			
Ifosfamide	800 mg/m²	IV 1 h			
PEG-Asparaginase	1000 U/m²	IV 2 h / IM			
Methotrexate	Age dep.	IT			
Cytarabine	Age dep.	IT			
Prednisolone	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

Criteria to start and guide the course

Start of the course requires neutrophils ≥0.5 x 10^9/L, platelets ≥50 x 10^9/L, and a clinical status allowing for treatment continuation. In case of prolonged treatment delays, dose reductions may be considered according to the specific guidelines outlined at chapter "General recommendations on chemotherapy" in page 19.

Diagnostic measures

Bone marrow aspirate at day 1 of week 11 is optional. It is recommended to assess cytological remission and MRD response in patients who were MRD positive at the previous time point.

Dexamethasone

10 mg/m²/d orally divided into two daily doses on days 1-6 of week 11.

Vincristine

1.5 mg/m² (maximum single dose 2 mg) as 15 min short infusion or as IV bolus (not on the same day as IT therapy) on days 1 and 6 of week 11.

Daunorubicin

30 mg/m^2 as 24-hour infusion on day 5 of week 11.

Methotrexate IV

1 g/m^2 i.v. over 36 hours starting on day 1 of week 5. 10% is given as a 30 min bolus and the remaining 90% as a continuous infusion over 35.5 hours. Concomitant alkaline hydration with 3000 ml/m^2/24 hours is given on day 1 and 2. Serum methotrexate levels can be measured at 36 hour and 48 hour after start of MTX infusion. Rescue with folinic acid at 15 mg/$m^2$is given at 48 and 54 hours after start of MTX. The dose can be adapted to elevated MTX serum levels. See further details under the chapter

"Impaired elimination of methotrexate" in page 39.

Ifosfamide
800 mg/m^2/dose as a 1-hour infusion every 12 hours on days 2-4 (total of 5 doses). Mesna at a dose of 300 mg/m^2 is given before start of infusion and 4 and 8 hours after start of infusion. Hydration with 3000 ml/m^2/d on days 2-5.

PEG-asparaginase
1,000 units/m² as a 2-hour infusion or intramuscularly on day 6 of week 11. The infusion of asparaginase should be started at a reduced rate and increased stepwise, if applicable. See further notes on alternative asparaginase agents at chapter "Asparaginase preparations" in page 37.

Intrathecal chemotherapy
Age adapted doses (see 5. Table in page 36) of methotrexate, cytarabine and prednisolone are administered on day 2 of week 11, directly before or up to 1 hour after start of the methotrexate infusion.

Local therapy

Radiation therapy

Radiation therapy is given to control disease in compartments protected from effective systemic chemotherapy by biologic blood barriers. This concerns CNS- and testicular relapse. Furthermore, in case of persistence of leukemia in other extramedullary sites such as mediastinum, lymph nodes, bone, skin, or other organs, a local radiation therapy may be necessary. This should be discussed individually with the national coordinating centers.

Radiation therapy is scheduled at the beginning of maintenance therapy in SR patients with extramedullary or combined medullary/extramedullary relapses not receiving SCT. Patients without extramedullary involvement at relapse are not to receive prophylactic irradiation.

Central nervous system relapse

Patients with a CNS relapse not eligible for allogeneic SCT receive irradiation of the cranium and the upper three cervical segments after completion of intensive chemotherapy. There is no clear evidence that craniospinal irradiation is superior to cranial irradiation. Particularly in isolated CNS relapse, however, there is a trend in favor of craniospinal irradiation. Craniospinal irradiation, therefore, is permitted. There is evidence to suggest that the use of thiopurines during cranial irradiation may predispose to the occurrence of brain tumors. Therefore, thiopurines are omitted during CNS irradiation. Children under 2 years of age with CNS disease at diagnosis are not eligible for cranial radiotherapy. They receive intrathecal therapy during maintenance therapy.

CNS irradiation is given at a dose of 18 Gy in daily fractions of 1.5 to maximum 2.0

Gy. If the interval to the first course of radiation therapy is shorter than 24 months or the previous radiation dose exceeds 15 Gy, then the radiation dose should be reduced to 15 Gy.

Testicular relapse

Local treatment of testicular relapse can be performed including orchiectomy and reduced irradiation of the contralateral non-involved testicle or including full dose irradiation of both testicles at the discretion of the treating center. Following a dose of 24 Gy, atrophy of the irradiated testis and absent endocrine function has to be expected. In case of allogeneic SCT, the orchiectomy should be performed at diagnosis or during early consolidation. In context of total body irradiation, the radiation dose given to the testes should be increased to 18 Gy giving a 6 Gy boost.

Option 1: Orchiectomy and reduced irradiation of the contralateral testicle
In case of a unilateral clinical involvement, the contralateral testis should be biopsied during the orchiectomy procedure. If the biopsy shows no involvement, local irradiation with 15 Gy is given. After this dose sufficient residual endocrine function is expected to allow the spontaneous onset of puberty. If the biopsy is positive or not performed, the clinically not involved testis should be irradiated with 18 Gy. If a clinically involved testis is not removed irradiation with 24 Gy should be performed.
Testicular involvement documented by ultrasound alone without clinical enlargement has to be confirmed by biopsy and will be treated like a clinically non-involved testis based exclusively on the result of the biopsy.

Option 2: Full dose irradiation of both testicles
Boys with testicular infiltration at presentation receive local irradiation of both testicles (irrespectively of the side and extent of involvement) with 24 Gy in 12 daily fractions.

Radiation technique and dose

Radiation therapy is principally performed using high-voltage technique (telecobalt or linear accelerator). The exact reproducibility of the daily positioning has to be ensured (for example using masks for immobilization).
During irradiation of the CNS individual attenuators have to be made to protect the visceral cranium and the anterior cervical soft tissues. The retroorbital spaces and the skull base have to be well included in the radiation field. If the entire neuroaxis is irradiated dosage gaps and overlaps of adjacent fields have to be avoided using divergence compensation. Due to the low lying frontal skull base in children under two years of age the protection of the eye lenses is not always possible. During follow-up regular ophthalmologic assessments, therefore, are required to detect and treat radiation cataracts in a timely manner. Emphasis is placed on a homogeneous distribution of the radiation dose. Principally, all fields are irradiated in each session. Single fraction should have a minimum dose of 1.5 Gy and a maximum dose of 2.0 Gy (1.8 Gy in children under the age of 2 years) and should be administered 5 times per week. To minimize the risk of leukoencephalopathy CNS irradiation is started only after the intensive phase of treatment is completed, i.e. after the last block.

Intrathecal chemotherapy

Patients will receive intrathecal chemotherapy at the time of the diagnostic lumbar puncture if the diagnosis of relapsed ALL is already confirmed at that time which then can be considered as the scheduled intrathecal therapy at the start of induction (day 1 of week 1). The schedule and dose of intrathecal chemotherapy is described in the chapters of the respective treatment arm.

Patients with CNS disease at diagnosis should receive weekly intrathecal chemotherapy according to the individual treatment arm until two consecutive clear CSF's have been obtained.

5. Table: Doses of triple intrathecal chemotherapy

Age [years]	methotrexate [mg]	cytarabine [mg]	prednisolone [mg]	0.9% NaCl [ml]
< 1	6	16	4	1.5
1	8	20	6	2.0
2	10	26	8	2.5
≥ 3	12	30	10	3.0

Orchiectomy

Orchiectomy is the most radical local therapy for a clinically involved testis. It can be performed as alternative (option 1,) to a local irradiation with 24 Gy (option 2) at the discretion of the treating center. The procedure is performed at the beginning of therapy if the clinical finding is unequivocal or during the course of therapy if histopathologic confirmation is required. In this case the decrease in size of the testis can be used as an indicator for the response to therapy. During orchiectomy or after termination of chemotherapy, a testicular prosthesis should be implanted. The hormonal dysfunction after orchiectomy or irradiation at 24 Gy is identical. The cosmetic result may be better compared to the testicular atrophy following local irradiation with 24 Gy. Subclinical involvement of the clinically not involved contralateral testis has to be excluded by biopsy, if a reduced local irradiation with 15 Gy in a non-involved and 18 Gy in a sub-clinically involved testis is intended. Depending on the result local irradiation is given accordingly.

New and alternative agents

Asparaginase preparations

This guidance advises for the use of PEG-asparaginase at first line.

In case of overt allergic reaction, one dose of PEG-asparaginase will be replaced by Erwinia-asparaginase at a dose of 20,000 units/m² IV or IM every 2nd day for a total of 6 doses if available in the given country.

Monitoring of asparaginase activity and antibodies is performed according to national agreements and is in case described in the national appendices.

In countries where PEG-asparaginase as first-line preparation is not available native E. coli-asparaginase may be given as first-line as long as it has been tolerated in previous treatments (4 doses given every 3rd day replacing 1 dose of PEG-asparaginase) at a dose of 10,000 units/m^2 on days 3 and 6 of week 1 and days 2 and 5 of week 2, calculated from the date PEG-asparaginase would be due.

Tyrosine kinase inhibitors

TKIs can be added to chemotherapy in all cases where genetic background supports their use (e.g. Philadelphia chromosome, ABL1 amplification, etc). Based on current expert opinion, imatinib should be chosen for Philadelphia chromosome patients even in cases when it was used in first line treatment. Second generation TKIs should be reserved to non-responders due to their severe toxicities when applied together with intensive chemotherapy.

Nelarabine

In patients with relapsed T-cell ALL, the use of nelarabine is left to discretion of each treating center. The suggested details of incorporation of nelarabine into the HR arm are listed in the appendix. There is an aim to unify the way nelarabine is applied, and its toxicities monitored if this drug is used. See Appendix 1.

Immune therapies

There is very intensive, promising research in this field, both with antibodies and cellular immune therapies. Evidence to support the use of some such therapy during first relapse treatment may emerge over the coming years. Availability of these treatment modalities will probably be heterogeneous among countries. This guidance does not direct or discourage the use of immunotherapy or its combination with standard chemotherapy.

Taking patients off treatment

We advise to take patients off protocol in the following situations:

- Standard risk patients not reaching hematological remission (≥M2 marrow) after cycle SC3;
- High risk patients with M2 marrow after cycle HC2.

The treating center can decide whether to enroll the patient in early clinical studies of new drugs, continue on protocol, choose any other treatment (e.g. cycles containing clofarabine or fludarabine, CAR-T cell therapy or blinatumomab, etc.) with curative intent or turn to palliation.

EMERGENCIES

The main problem of intensive multi-agent chemotherapy is the combination of direct organ and mucosal toxicity and marked immunosuppression which may result in serious infections. A number of protective and supportive measures are urgently required to prevent potentially serious harm associated with therapy.

Acute tumor lysis syndrome

The acute tumor lysis syndrome is rare in children with relapsed ALL, since this type of leukemia in general is relatively resistant to therapy. During the lysis of leukemic cells the purine degradation products xanthine, hypoxanthine and uric acid as well potassium and phosphate are released. A rapid lysis of large cell numbers may result in precipitation within the renal tubules and collecting ducts and in life-threatening hyperkalemia. To prevent acute tumor lysis syndrome, forced diuresis with 3-6 $L/m^2/d$ (the fluid balance is maintained with furosemide as needed), and allopurinol (at a dose of 10 $mg/m^2/day$) are used. In case of hyperuricemia, beginning renal insufficiency or marked hyperleukocytosis treatment with rasburicase may be indicated. In case of marked hyperkalemia, hyperphosphatemia, hyperuricema or renal insufficiency, hemodialysis may become necessary.

Impaired elimination of methotrexate

It is advisable to measure methotrexate levels after the MHD IV MTX infusions. The serum methotrexate level 48 hours after the start of methotrexate infusion is generally below 0.5 µmol/L. Otherwise, folinic acid rescue is extended at six hourly intervals beyond the scheduled doses at 48 and 54 hours, until the methotrexate level falls below 0.25 µmol/L. The dose of folinic acid depends on the methotrexate level and is calculated as 15 mg/m^2 antagonizing up to 1 µmol/L serum methotrexate. If the methotrexate level at 48 hours is > 2.0 µmol/L, alkaline diuresis with 3 to 4.5 L/m^2 is used in addition. If the methotrexate level at 48 hour is > 5 µmol/L or in cases of marked intolerance with severe vomiting, diarrhea and neurological symptoms, the use of carboxypeptidase should be considered. Carboxypeptidase results in enzymatic cleavage of methotrexate. In this case, contact the national or international study coordinator. If a decreased elimination of methotrexate is apparent at 36 hours (MTX level > 10 µmol/L), a methotrexate serum level at 42 hours is recommended. In this case the administration of leucovorin should be adjusted to a dose equivalent to that recommended by the rescue scheme at 42 hours (15 mg/m^2 antagonizing up to 1 µmol/l serum methotrexate). If the value is > 5 µmol/L, the dose of folinic acid is calculated using the following formula:
leucovorin (mg) = MTX at 42h (µmol/L) x body weight (kg).

Extravasation of anthracyclines or vinca alkaloids

In case of extravasation of an anthracycline, the extravasate as well as the tissue fluid and blood should first be aspirated, using the existing venous access and, if possible, diluted by instilling normal saline before removing the vascular line. Topical applica-

tion of dimethylsulfoxide (DMSO 99%) four drops per 10 cm^2 skin three times a day for several days may ameliorate the course. The local area of skin should be kept cool for several days.

In case of extravasation of a vinca alkaloid, the extravasate as well as tissue fluid and blood should be aspirated, using the existing venous access. Then hyaluronidase (150 units/mL NaCl 0.9%) should be injected into that area using the existing venous access before removing it. Subsequently, the affected tissue can be infiltrated subcutaneously with several small injections of hyaluronidase. The local area should be kept warm (in contrast to the cooling recommended for anthracycline extravasations). If necrosis develops despite these local measures, early surgical revision should be considered.

SUPPORTIVE CARE

Supportive care is performed according to national and local guidelines. A regular pneumocystis carinii prophylaxis is recommended as well as an effective antimycotic prophylaxis.

Anti-infectious Prophylaxis
From the start of treatment until the end of maintenance or until SCT the following measures may optionally be applied (for supportive care during SCT see SCT protocols):

Pneumocystis carinii prophylaxis:
Cotrimoxazole, 2-3 mg/kg trimethoprime (10-15 mg/kg sulfamethoxazole) BID on 2 days per week (e.g. Saturday and Sunday). The drug should not be given the same day as methotrexate. Cotrimoxazole may cause prolonged cytopenias. If this is suspected, the drug should be interrupted or discontinued. As an alternative inhalation with pentamidine 300 mg once a month or Dapsone 4 mg/kg weekly needs to be considered.

Antifungal prophylaxis:

Amphotericin B suspension for local (oral mucosa and upper GI tract) candida prophylaxis:
The amphotericin suspension is carefully spread over the entire oral mucosa and then swallowed. If prophylaxis with amphotericin suspension is not feasible or if thrush becomes apparent despite prophylaxis, fluconazole (2 mg/kg/d) is recommended. Hepatic toxicity and possible drug resistance have to be considered.

Systemic antimycotic prophylaxis
In case of prolonged aplasia, systemic antifungal prophylaxis according to preferences at the different centers may be applied. Schemes such as daily oral voriconazole or intermittent liposomal amphotericin-B 3x/week have been applied.

Anti-emetic treatment
Ondansetron (two doses of 5 mg/m^2/day) may be used for highly emetogenic treatment elements such as high-dose Ara-C, ifosfamide and cyclophosphamide. Additional treatment with aprepitant or dimenhydrinate may be required, if that agent is insufficient particularly in adolescents. Many treatment elements already include the administration of dexamethasone, so that no further anti-emetic effect can be expected from this agent.

Febrile Neutropenia
In case of a neutrophil count below 0.5 x 10^9/L and fever greater than 38.5 °C systematic antibiotic and possibly anti-fungal treatment has to be administered. Particularly patients with a high therapeutic risk (e.g. patients with very early relapse during initial treatment or fever at the beginning of cytopenia) require rapid escalation of antibiotics to be able to control severe infections until the regeneration of cells.

APPENDIX 1: Nelarabine

Introduction
Giving nelarabine is an optional addition to the therapy of T-ALL relapses. Nelarabine is not available in all ALL-IC countries, and different regulations apply to various ALL-IC countries. The European Medical Agency (EMA) and the US Food and Drug Administration Agency (FDA) licensed nelarabine for third line treatment of acute lymphoblastic leukemia and acute lymphoblastic lymphoma. There are studies suggesting that it is effective in these diseases, but, to our knowledge, no large randomized study has been or is being conducted to help in shaping and evaluating its application. Here we suggest a possible way of its application based on best available published and unpublished data. Taking in consideration the bleak outlook of high risk T-ALL relapses with poor early response to treatment, also the potentially severe neurotoxicity and high costs associated with nelarabine, the treating centers will consider this option and decide on its use.

To learn as much as possible, we suggest administering nelarabine in a standardized way and monitoring its toxicity. The aim is to gather and publish these data. Please contact Daniel Erdelyi (erdelyi.daniel@med.semmelweis-univ.hu) to provide data if applying this part of the guidance. Toxicity monitoring is of great importance.

Suggested target population
T-cell ALL patients on the high risk arm with poor early treatment response, as defined by MRD $\geq 0.1\%$ at the end of induction.

Schedule and administration:
Up to three nelarabine courses can be inserted into the high risk arm. These five-day-long courses should be given before HC1, HC2 and HC3. The criteria to start and guide the combined nelarabine-HC1/2/3 courses are the same as those described as starting criteria of each HC cycle. When nelarabine is given on days 1-5, drugs of the HC cycle should be administered starting on day 8. No blood count criteria should be considered on day 8 to continue with the original HC cycle. However, treatment should be interrupted in case of any neurotoxicity CTC grade 3 or over, or in case of any other newly appearing severe toxicity.

Nelarabine dosing: 650 mg/m^2 as two-hour-long infusion daily on five consecutive days. No hyperhydration is required.

Warning
Intrathecal chemotherapy must not be administered between day -1 and day 6 of the nelarabine course! I.th. chemotherapy during i.v. nelarabine treatment is thought to increase the risk of severe, even life threatening central nervous system toxicity.

APPENDIX 2: High risk definitions in the IntReALL studies

The IntReALL study group stratifies some certain genetic subgroups as high risk regardless of other prognostic factors. The basic principle is to treat patients with less than 30% long term survival chance on the HR arm and assign them to SCT.

This is a rapidly developing field; changes in the definitions are expected now and again. The list below shows the additional high risk definitions for first ALL-relapses, received from the I-BFM Resistant Disease Commitee as per May 2017:

- near haploidy, hypodiploidy (≤44 chromosomes)
- t(1;19) *TCF3/PBX1*
- t(17;19) *TCF3/HLF*
- *TP53* mutations or deletion
- *NT5C2* mutations

Further subgroups from the committee, though without full agreement or conviction:

- MLL rearrangements
- iAMP21

Our ALL-IC REL group also suggests high risk stratification of these relapsed patients:

- Philadelphia chromosome
- ABL1 amplification (especially when relapsed post TKI)

APPENDIX 3: Data capture forms

Registration form / ALL-IC REL 2016 registry

Country_____ Hospital _____ Patient Unique Number (PUN)_____

Surname: _____ Given name: _____ Date of birth: _____
(Please write all dates in this format: YYYY – Mmm – DD e.g. 2017 – June – 05)

sex: ☐ male ☐ female
Down Syndrome: ☐ yes ☐ no

Consent for inclusion in registry:
☐ agreement
☐ only after additional information
☐ against participation

CHECKLIST: date when forms were sent:

At diagnosis:

- registration form _____
- bone marrow results _____

During the intensive phase of treatment:

Strategic group 1 to 4 / arm A and B

- copy of toxicity forms, **all** courses (with individual dose) _____
- bone marrow results _____
- stem cell transplantation form _____
- local therapy form _____

During follow-up

- subsequent events _____
- report of severe adverse events _____

DATA REGARDING THE PRIMARY THERAPY OF ALL

Date of diagnosis: _____ Treatment protocol: ☐ ALL IC-BFM 2009 ☐ other, specify_____

Treatment arm _____

Immunophenotype: ☐ pre-B ☐ T ☐ MPAL ☐ other, specify: _____

CNS involvement: ☐ CNS1 ☐ CNS2 ☐ CNS3 ☐ unknown;

Testicular involvement: ☐ yes ☐ no ☐ unknown

Radiation therapy: ☐ yes, dose [Gy] _____ ☐ no ☐ cranial ☐ craniospinal ☐ TBI

Treatment completed: ☐ yes ☐ no ; Last day of treatment: _____

Molecular studies: BCR/ABL ☐ yes ☐ no ☐ unknown; TEL/AML1 ☐ yes ☐ no ☐ unknown;

MLL-abnormality ☐ yes ☐ no ☐ unknown; Other: _____

CURRENT RELAPSE

date of diagnosis: _____ site: ☐ BM ☐ CNS ☐ testes ☐ other _____

BM involvement: ☐ ≥25%; ☐ 5-24,99%; ☐ <5% but MRD pos; ☐ MRD neg

white cell count: _____ G/L

periph blood blast: _____ %

CNS stage: ☐ CNS1 ☐ CNS2 ☐ CNS3

LEFT TESTIS:
Clinical involvement ☐yes ☐no
☐ not biopsied
☐ biopsied – pos. histopathology
☐ biopsied – not affected

RIGHT TESTIS:
Clinical involvement ☐yes ☐no
☐ not biopsied
☐ biopsied – pos. histopathology
☐ biopsied – not affected

Time point:
☐ late ☐ early ☐ very early

start of treatment: _____

Risk group: ☐SR ☐HR

Any major deviation from treatment protocol?
(e.g. cycles or drugs omitted, drug doses reduced)
☐ no ☐ yes, explain: …

date: _____ signature: _____

Bone marrow results / ALL-IC REL 2016 registry

Country_____ Patient Unique Number (PUN)_____

PUNCTURE AFTER SI-BLOCK (DAY 29)

Date of BMP: _____ Blasts bone marrow (%) by morphology: _____by flow:_____

Mark representative Cellular content Regeneration cells
☐ yes ☐ increased (hyperplastic) ☐ complete
☐ no ☐ normal ☐ commencing
☐ doubtful ☐ reduced (hypoplastic) ☐ absent
☐ aplastic ☐ not eligible

If repeated at later time point:

Date of BMP: _____ Blasts bone marrow (%) by morphology: _____by flow:_____

Mark representative Cellular content Regeneration cells
☐ yes ☐ increased (hyperplastic) ☐ complete
☐ no ☐ normal ☐ commencing
☐ doubtful ☐ reduced (hypoplastic) ☐ absent
☐ aplastic ☐ not eligible

PUNCTURE BEFORE SC3-BLOCK (SR PATIENTS ONLY)

Date of BMP: _____ Blasts bone marrow (%) by morphology: _____by flow:_____

Mark representative Cellular content Regeneration cells
☐ yes ☐ increased (hyperplastic) ☐ complete
☐ no ☐ normal ☐ commencing
☐ doubtful ☐ reduced (hypoplastic) ☐ absent
☐ aplastic ☐ not eligible

PUNCTURE BEFORE SCT (SCT PATIENTS ONLY)

Date of BMP: _____ Blasts bone marrow (%) by morphology: _____by flow:_____

Mark representative Cellular content Regeneration cells
☐ yes ☐ increased (hyperplastic) ☐ complete
☐ no ☐ normal ☐ commencing
☐ doubtful ☐ reduced (hypoplastic) ☐ absent
☐ aplastic ☐ not eligible

date: _____ signature: _____

Toxicity form / ALL-IC REL 2016 registry

Please fill after each cycle of chemotherapy

Country_____ Patient Unique Number (PUN)_____

Toxicity following treatment cycle, with starting date: _____

arm SR: ☐ SI ☐ SC1 ☐ SC2 ☐ SC3 ☐ SC4 ☐ SC5 ☐ SC6 ☐ SC7

arm HR: ☐ HI ☐ HC1 ☐ HC2 ☐ HC3 ☐ with nelarabine

Any modification from protocol in this cycle? ☐ no ☐ yes, explain: _____

Poorest Karnofsky/Lansky score: _____

CTC GRADE	0	1	2	3	4	5	unknown /comment
Infection	none	minor	moderate, nor organ-ism, on iv antibiotics	severe, organ-ism isolated, on iv antibiot-ics	life-threatening with hypo-tension	cause of death	
stomtatitis	none	painless ulcers, erythema	painful ery-thema or ulcers; able to eat	painful ery-thema or ul-cersations; unable to eat	TPN required due to sto-matitis	-	
diarrhoea	none	<4/day	< 7 also at night, mild cramping	< 10 inconti-nence, severe cramping	≥ 10 or bloody diarr-hea, TPN required	-	
creatinine	normal for age	≤ 1.5 x ULN	≤ 3 x ULN	≤ 6 x ULN	> 6 x ULN	death due to renal failure	
bilirubin	normal for age	≤ 1.5 x ULN	≤ 3 x ULN	≤ 10 x ULN	> 10 x ULN	death due to liver failure	
peripheral neuro-pathy	none	asympto-matic; only diagnostic observation	moderate	limiting self care; assistive device indi-cated	life-threatening	-	

TOXICITY	yes	no	unkown	comment
heart failure (linEF<28%)				
arrhythmia				
CNS complications, e.g. seizure, PRES, focal neurol. signs, altered conscious-ness, psychosis, depression				
hypertension requiring treatment				
steroid diabetes (needing insulin)				
thrombosis				
major bleed				
pancreatitis				
paralytic ileus				
sinusoidal obstruction syndrome (VOD)				
intensive care unit admission				

Comments / other complications / drug intolerance:

date: _____ signature: _____

Stem cell transplantation / ALL-IC REL 2016 registry

Country_____ Patient Unique Number (PUN)_____

Has SCT been performed? yes ☐ no

TYPE OF SCT
- ☐ no transplantation
- ☐ MSD
- ☐ MFD >= 9/10 AG
- ☐ MUD >= 9/10 AG
- ☐ MMFD < 9/10 AG
- ☐ MMUD < 9/10 AG
- ☐ haplo FD
- ☐ autologous
- ☐ FD, unknown HLA typing
- ☐ UD, unknown HLA typing

IF NO SCT, REASON
- ☐ no indication
- ☐ no appropriate donor
- ☐ previous disease
- ☐ progression of ALL
- ☐ toxicity of ALL relapse therapy
- ☐ no compliance by parents or ☐ syngen patient
- ☐ further _____

CONDITIONING PHASE
- ☐ none
- ☐ VP16 and TBI
- ☐ other and TBI
- ☐ BU/VP16
- ☐ other (Specify_____)

DATE OF SCT: _____ , if timing was different from protocol recommendation, then

please comment: _____

date: _____ signature: _____

Local therapy / ALL-IC REL 2016 registry

Country_____ Patient Unique Number (PUN)_____

RADIATION THERAPY GIVEN? ☐ yes ☐ no

Beginning of CNS radiation, date _____

Type of CNS radiation ☐ cranial ☐ cranio-spinal

Dose of CNS radiation (Gy) _____

Beginning testis radiation, date _____

Type of testis radiation ☐ right ☐ left ☐ left and right

Dose of testis radiation (Gy) right: _____ left: _____

Beginning of other site radiation, date _____

Site _____

Dose of other site radiation (Gy) _____

Beginning of TBI, date _____

Dose of TBI (Gy) _____

ORCHIECTOMY PERFORMED?

☐ left testis
☐ right testis
☐ both sides
☐ not done

Date orchiectomy _____

date: _____ signature: _____

Subsequent events / ALL-IC REL 2016 registry

Country_____ Patient Unique Number (PUN)_____

Date of last check-up_____

SUBSEQUENT RELAPSE ☐ yes ☐ no

date:_____ site ☐ BM ☐ CNS ☐ testis ☐ Other _____

Blasts bone marrow (%) by morphology: _____ by flow: _____

Is further treatment planned ? ☐ no ☐ yes, which protocol ? _____

SECOND MALIGNANCY ☐ no ☐ yes, date:_____

☐ ALL ☐ NHL ☐ AML ☐ MDS ☐ brain tumor ☐ osteogenic sarcoma ☐ other tumor ___

DEATH ☐ yes ☐ no

date of death:_____ ; was the patient in remission? ☐ yes ☐ no ☐ unknown

cause of death:
- ☐ related to relapse
- ☐ related to treatment complication
- ☐ related to BMT
- ☐ related to a second malignancy
- ☐ during induction, remission status unknown

comment: _____

TERMINATION OF TREATMENT

date:_____ Time point within the protocol: _____

reason: _____

LONG TERM COMPLICATIONS

neurological:	☐ no	☐ yes,	explain:_____
bone:	☐ no	☐ yes,	explain:_____
heart:	☐ no	☐ yes,	explain:_____
renal:	☐ no	☐ yes,	explain:_____
other:	☐ no	☐ yes,	explain:_____

date: _____ signature: _____

Report of a severe adverse event / ALL-IC REL 2016 registry

Severe adverse events are defined as follows:
- ◆ each death independent of cause that occurs during or up to 6 weeks after the completion of protocol therapy
- ◆ life-threatening disease
- ◆ events resulting in permanent disability

Date of event: _____

Description of the event (type, onset, duration, extent, severity):

Causality:

Is the pre-existing condition of the patient or an unrelated disease responsible for this event ?

☐ yes ☐ probable ☐ possible ☐ improbable ☐ no

Do you think the event is related to protocol therapy?

☐ yes ☐ probable ☐ possible ☐ improbable ☐ no

date: _____ signature: _____