Randomized trial of radiation-free central nervous system prophylaxis comparing intrathecal triple therapy with liposomal cytarabine in acute lymphoblastic leukemia

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Online Supplement

Containing the following items relative to NILG ALL study 10/07:

A. ALL diagnosis and subclassification
B. Treatment protocol details
    a. Patient eligibility to the study
    b. Definitions of risk subsets
    c. MRD study
    d. Drug dosage and scheduling per treatment cycle
    e. Final MRD and risk-oriented treatment strategy
C. Detailed neurotoxicity results from CNS prophylaxis trial

A. ALL diagnosis and subclassification

The early diagnostic work must be completed in 24-48 hours, in order to allow rapid recognition of eligible cases and registration into study, and must provide the clinician with the following informations:

- Diagnosis of ALL with exclusion of AML/other neoplasms
- Diagnosis of ALL subtype

Diagnostic methodology at presentation is based on jont BM/PB analysis through morphology, cytochemistry and immunophenotype. Cytogenetics and molecular biology studies are of course carried out, but their results are known at a later stage and therefore do not assist in the early diagnostic evaluation. These tests must be applied in an integrated and perfectioned fashion as indicated by major consensus papers of FAB, WHO and EGIL groups:

1. JM Bennett et al. Proposals for the classification of the acute leukaemias. *Br J Haematol 1976; 33: 451.*
2. JM Bennett et al. The morphological classification of acute lymphoblastic leukaemia: concordance among observers and clinical correlations. *Br J Haematol 1981; 47: 553*
3. MC Bene et al. Proposals for the immunological classification of acute leukemias. *Leukemia 1995;9:1783.*
4. Consensual European immunophenotyping panels for leukaemia – 6th PCRDT, april 23, 2005. Obtainable at URL www.leukemia-net.org, select "diagnostics" in the upper menu bar, select again " diagnostics" in the new page, left column: standards/SOP's of Project 10 will appear automatically.
5. ES Jaffe et al. WHO classification of tumours - Tumours of haematopoietic and lymphoid tissue. IARC Press. Lyon 2001.

Because widely employed and promptly applicable to newly diagnosed patients with ALL, FAB terminology will be retained in the current study for general diagnostic purposes and study registration. The new EGIL/WHO diagnostic terminology will be added to each case following the results of immunophenotype, cytogenetics etc.

Diagnostic material and tests:

- A core marrow biopsy is necessary when marrow aspiration is difficult and/or hypocellular.
- In BM/PB samples, ALL is initially identified according to FAB criteria. However, differing from the L3 subtype that is typcally associated with Burkitt leukemia, the distinction between L1 and L2 is currently of little practical relevance.
- For correct identification of ALL features, both BM cells and PB cells should be evaluated.
- By **morphology**/**cytochemistry**, ALL cells are usually Sudan black B (SBB) and myeloperoxydase (MPO) negative, though SBB+ ALL and/or "granular" ALL is occasionally reported.
- The **immunophenotype panel** includes all necessary reagents to obtain the relevant informations and to discriminate ALL from AML/other disease.

Table: ALL diagnostics by immunophenotype

Purpose	**CD antigens (c=cytoplasmic; Tdt=nuclear)**
Gating of non-erythroid cells and differential vs. nonhematologic	CD45 (pos)
Differential vs. AML	cMPO, CD117 (neg, CD117 rare T-lineage pos) vs. cCD22, cCD79a (pos B-lineage) cCD3 (pos T-lineage)
Establish ALL subset	
pro-B (B-I)	CD19 and/or cCD79a and/or cCD22
"common" (B-II)	plus CD10 (>10%)
pre-B (B-III)	plus cIgM+
T-lineage pro-T (T-I)	cCD3 and CD7
T-lineage pre-T (T-II)	plus CD2 and/or CD5 and/or CD8
T-lineage cortical (T-III)	plus CD1a+
T-lineage mature (T-IV)	plus CD3+, CD1a-
Additional markers	TdT CD24 (B-lineage) anti-TCR (T-lineage) CD34, CD13, CD33, CD15, anti-MPO, CD64, CDw65 (stem cell/myeloid)

Cases with <25% lymphoid blast cells in the bone marrow and a definite histopathologic diagnosis of lymphoblastic lymphoma in a lymphnode or other extramedullary tissue are better referred to as such (LL). Data from morphological and immunophenotypic assessment will be integrated by cytogenetics (and FISH) plus molecular biology tests, in order to indentify specific ALL syndromes within each immunophenotypic subgroup:

Cytogenetics, FISH and molecular biology

The following abnormalities will be looked for and registered for the purposes of the current study (standard banding technique or FISH or molecular biology are considered equivalent):

- t(9;22) or *BCR-ABL1* rearrangement
- t(4;11) or *AF4-MLL* rearrangement
- t(1;19) or *PBX/E2A* rearrangement
- t(12;21) or *TEL-AML1* rearrangement
- -7, +8, del6q, t(8;14), other MLL rearrangement at 11q23
- Hyperdiploid (>50) ALL

- Low hypodiploid with 30-39 chromosomes
- Near triploid with 60-78 chromosomes
- Complex with ≥5 unrelated clonal abnormalities
- Hyperdiploid (>50 chromosomes)
- Other

B. Treatment protocol details

PATIENTS	Adult patients with ALL as per inclusion/exclusion criteria. All patients aged 18+ years will be included in the ALL Prospective Register.
STUDY DESIGN	**NILG-ALL 10/07 Trial** Multicentric prospective pilot randomized phase II trial on CNS prophylaxis with liposomal cytarabine (DepoCyte) vs. standard intrathecal injections. All patients receive induction/consolidation therapy incorporating lineage-targeted high-dose methotrexate plus other drugs (with additional imatinib in Ph/BCR-ABL+ ALL), for the achievement of an early negative MRD status. The MRD study supports a risk/MRD-oriented final consolidation phase. **Risk Classification** Newly diagnosed patients are hierarchically clustered into very high, high and standard risk cases (VHR, HR, SR) using international risk criteria modified according to NILG: ▪ **VHR (any criterium):** B-precursor: WBC count >$100x10^9$/L; adverse cytogenetics/molecular biology such as t(9;22)/BCR-ABL, t(4;11)/MLL rearrangement at 11q23, +8, -7, del6q, t(8;14), low hypodiploidy with 30-39 chromosomes, near triploidy with 60-78 chromosomes, complex with ≥5 unrelated anomalies. T-precursor: WBC count >$100x10^9$/L; early/late non-cortical immunophenotype (CD1a-); adverse cytogenetics/molecular biology (as above). ▪ **HR (any criterium, VHR excluded)**: B-precursor: WBC count >$30x10^9$/L; pro-B immunophenotype; complete remission after cycle 2. T-precursor: complete remission after cycle 2. ▪ **SR (all criteria, VHR/HR excluded):** B-precursor: WBC count <$30x10^9$/L; T-precursor: WBC count <$100x10^9$/L; cortical immunophenotype (CD1a+). **CNS Prophylaxis** **Stratification before randomisation** • by immunophenotype, i.e. B-precursor vs. T-precursor • by risk class, i.e. SR vs. non-SR (using only known factors) **Randomisation:** intrathecal (IT) CNS prophylaxis with standard triple therapy (TIT, 12 total injections) vs. DepoCyte (6-8 total injections by disease subset). Cranial irradiation is omitted in both arms, and all patients receive the same chemotherapy program including CNS-crossing agents. **Induction/Early Consolidation and MRD Study** Randomised patients receive homogeneous induction/early consolidation chemotherapy, with concurrent MRD analysis at four timepoints (weeks 4, 10, 16 and 22 of induction/consolidation), to optimize risk classification and support risk/MRD-oriented therapy: • **MRD negative (M-NEG):** negative MRD study (<10^{-4} at timepoints #2 and #3, and negative at timepoint #4) • **MRD positive (M-POS):** positive MRD study (≥10^{-4} at timepoints #2 or #3, or positive at timepoint #4)

	<u>MRD/Risk-Oriented Final Therapy</u> • **VHR** patients are candidate to an early allogeneic SCT (related/unrelated donor/cord blood; ablative/non-ablative conditioning according to current protocols/guidelines) after CR, regardless MRD study results. • **M-POS** as well as **HR** patients with unknown MRD are allocated to allogeneic SCT after MRD timepoint 2 (M-POS $\geq 10^{-4}$) or MRD timepoint 4 (others). When an allogeneic SCT is not possible, patients complete consolidation and receive autologous-type SCT followed by maintenance. • **M-NEG** as well as **SR** patients with unknown MRD are allocated to maintenance therapy. **Age-limited therapeutic procedures**: Patients aged >55 years are treated with age-adapted therapy, and when indicated will be included in SCT programs whenever possible and according to performance status and comorbidity.
STUDY POPULATION	**Inclusion criteria** • Age 18-65 years. • Diagnosis of untreated ALL with B-/T-precursor phenotype, either *de novo* or secondary to chemo-radiotherapy for other cancer. • Full cytological, cytochemical, cytogenetic and immunobiological disease characterization by revised FAB, EGIL and WHO criteria. • Bone marrow and peripheral blood sampling for MRD study. • ECOG performance status 0-2 or reversible ECOG 3 score following intensive care of complications. • Signed informed consent. **Exclusion criteria** • Diagnosis of B-ALL (FAB L3 ALL/Burkitt's leukemia).. • Down's syndrome. • Pre-existing, uncontrolled pathology such as cardiac disease (congestive/ischemic, acute myocardial infarction within the past 3 months, untreatable arrythmias, NYHA classes III and IV), severe liver disease with serum bilirubin >3 mg/dL and/or ALT >3 x upper normal limit (unless attributable to ALL/LL), kidney function impairment with serum creatinine >2 mg/dL (unless attributable to ALL/LL), and severe neurological or psychiatric disorder that impairs the patient's ability to understand and sign the informed consent, or to cope with the intended treatment plan. • Known HIV positive serology. • Other active hematological or non-hematological cancer with life expectancy <1 year. • Pregnancy (fertile women will be advised not to become pregnant while on treatment; and male patients to adopt contraceptive methods), unless therapeutic aborption/early discharge is carried out.
	CNS prophylaxis (Randomisation) Standard TIT or DepoCyte are administered during induction/consolidation/maintenance. CR patients continue CNS prophylaxis until relapse in any site or allogeneic/autologous SCT.

TREATMENT AND STUDY DRUGS	**Standard arm** **TIT** (triple IT therapy) with methotrexate 12.5 mg, cytarabine 50 mg, prednisone 40 mg/dexamethasone 4 mg on: • days 1 and 15 of induction/consolidation cycles 1, 2 and 8; • day 1 of consolidation cycles 4 and 6; • day 1 of maintenance cycles 2, 3, 4 and 5. (total no. 12) Patients with CNS involvement at diagnosis: TIT with methotrexate 15 mg, cytarabine 75 mg, prednisone 40 mg bi-weekly until CNS remission, followed by weekly x2 and monthly x12 (except during consolidation cycles 3, 5 and 7). **Experimental arm** Dexamethasone 4 mg, **DepoCyte** 50 mg IT on: • day 1 of induction/consolidation cycles 1, 2, 4, 6, 8; • day 15 of induction/consolidation cycles 1 and 8 (only T-ALL); • day 1 of maintenance cycle 2 . (total DepoCyte no. 6 and 8 for B- and T-lineage ALL/LL, respectively) Patients with CNS involvement at diagnosis: Dexamethasone 4 mg, DepoCyte 50 mg IT on days 1 and 15 of induction/consolidation cycles 1 and 8, day 1 of consolidation cycles 2, 4 and 6, and day 1 of maintenance cycles 2, 4 and 6 (total 10 doses in all patients). **Lineage–Targeted Induction/Consolidation Therapy** Including subset-specific elements for B-precursor ALL (3x targeted-infusion methotrexate 2.5 g/m^2), T-precursor ALL (3x targeted-infusion methotrexate 5 g/m^2), age >55 years (methotrexate reduced to 1.5 g/m^2), Ph/BCR-ABL+ ALL (imatinib, reduced-intensity chemotherapy). Patients not in CR after cycles 1-2 are off study. For CR evaluation bone marrow is checked on days 28 and/or 56. Consolidation cycles are administered at 21-28 day intervals. **Induction/early consolidation therapy** • *Cycle 1*: prednisone 20 mg/m^2/bd PO (per os) on days -5 to -1, cyclophosphamide 300 mg/m^2/d IV (intravenous) on days -3 to –1 (pre-induction); idarubicin 12 mg/m^2/d IV on days 1 and 2, vincristine 1.4 mg/m^2/d (max. 2 mg) on days 1, 8, 15 and 22, L-asparaginase (E.Coli) 3.000 U/m^2 IV on days 8, 10, 12, 15, 17 and 19, dexamethasone 5 mg/m^2/bd IV on days 1-5, 15-19, G-CSF from day 5 (induction). • *Cycle 2:* idarubicin 12 mg/m^2/d IV on day 1, cyclophosphamide 1000 mg/m^2 IV on day 1, dexamethasone 5 mg/m^2/bd IV/PO on days 1-5, cytarabine 75 mg/m^2/d IV/SC (subcutaneous) on days 2-5, 6-mercaptopurine 60 mg/m^2/d PO on days 1-10, G-CSF from day 8 to resolution of absolute neutropenia <1 $x10^9$/L. • *Cycles 3,7*: methotrexate 2.5/5 (B/T phenotype) g/m^2/d IV on day 1 (24-h infusion, folinic acid rescue), cytarabine 2 g/m^2/bd IV on days 3 and 4, G-CSF

	from day 8 (collection/cryopreservation of autologous blood stem cells at cycle 3). • *Cycles 4,6:* idarubicin 12 mg/m^2/d IV on day 1, cyclophosphamide 1000 mg/m^2 IV on day 1, vincristine 1.4 mg/m^2/d (max. 2 mg) IV on days 1 and 8, dexamethasone 5 mg/m^2/bd IV/PO on days 1-5, cytarabine 75 mg/m^2/d IV/SC (subcutaneous) on days 2-5, 6-mercaptopurine 60 mg/m^2/d PO on days 1-10, G-CSF from day 8 to resolution of absolute neutropenia <1 x10^9/L. • *Cycle 5:* methotrexate 2.5/5 (B/T phenotype) g/m^2/d IV on day 1 (24-h infusion, folinic acid rescue), L-asparaginase (E. Coli) 10.000 U/m^2 IV on days 3 and 8. • *Cycle 8:* idarubicin 10 mg/m^2/d IV on days 1 and 8, vincristine 1.4 mg/m^2/d (max. 2 mg) IV on days 1 and 8, cyclophosphamide 300 mg/m^2/d IV on days 1-3, dexamethasone 5 mg/m^2/bd IV/PO on days 1-5, prednisone 20 mg/m^2/bd PO on days 8-12, G-CSF from neutropenia <0.5 microl to its resolution. <u>Variations for Ph/BCR-ABL+ ALL</u>: • *Cycle 1*: imatinib 400 mg/bd PO on days 1-28, idarubicin on day 1 only, L-asparaginase omitted. • *Cycle 2*: imatinib 400 mg/bd PO on days 1-21, idarubicin 10 mg/m^2, cyclophosphamide 650 mg/m^2, cytarabine on days 2-5 only, 6-mercaptopurine on days 1-7 only. • *Cycles 3, 7*: imatinib 400 mg/bd PO on days 8-21, methotrexate 1.5 g/m^2. • *Cycles 4, 6*: imatinib 400 mg/bd PO on days 8-21, idarubicin 10 mg/m^2, cyclophosphamide 650 mg/m^2, vincristine on day 1 only, cytarabine on days 2-5 only, 6-mercaptopurine on days 1-7 only. • Cycle 5: imatinib 400 mg/bd PO on days 8-21, methotrexate 1.5 g/m^2. • *Cycle 8*: imatinib 400 mg/bd PO on days 8-21, idarubicin on day 1 only, cyclophosphamide omitted. <u>Variations for age >55 years (all subtypes)</u>: • *Cycles 3, 7*: methotrexate 1.5 g/m^2. • *Cycle 5*: methotrexate 1.5 g/m^2. **MRD/Risk-Oriented Therapy** **<u>M-NEG/SR patients: Maintenance (24 4-week cycles)</u>** • *Cycles 1, 3, 5, 7, 9, 11*: cyclophosphamide 100 mg/m^2/d PO on days 1-4, 6-mercaptopurine 75 mg/m^2/d PO on days 8-28, methotrexate 15 mg/m^2/d PO/IM (intramuscular) on days 8, 15 and 22. • *Cycles 2, 4, 6, 8, 10, 12:* vincristine 1 mg/m^2 IV on day 1, prednisone 40 mg/m^2/d PO on days 1-5, 6-mercaptopurine 75 mg/m^2/d PO on days 8-28, methotrexate 15 mg/m^2/d PO/IM on days 8, 15 and 22. • *Cycles 13-24:* 6-mercaptopurine 75 mg/m^2/d PO on days 1-28, methotrexate 15 mg/m^2/d PO/IM on days 1, 8, 15 and 22. **<u>M-POS/HR and VHR patients: 1st option Allogeneic SCT</u>** • *Allogeneic SCT:* first choice option, from sibling/unrelated donor or cord blood. SCT procedure by local guidelines/protocols. SCT timing is by risk class (VHR:

	early) and MRD study results (positive timepoint 2: early; others: at end of consolidation, with interim maintenance). **<u>M-POS/HR and VHR patients: 2nd option Autologous SCT with Maintenance (12 4-week cycles)</u>** • *Autologous SCT*: second choice option if allogeneic SCT not possible (NB: maintenance only if autologous SCT not feasible), with melphalan 100 mg/m^2/d IV on days 1 and 2, plus unpurged autologous CD34+ blood cells (2-6x10^6/kg) on day 4, and G-CSF. • *Maintenance cycles 1, 3, 5, 7, 9, 11:* cytarabine 300 mg/m^2 IV on day 1, cyclophosphamide 100 mg/m^2/d PO on days 1-4, 6-mercaptopurine 75 mg/m^2/d PO on days 8-28, methotrexate 15 mg/m^2/d PO/IM on days 8, 15 and 22. • *Maintenance cycles 2, 4, 6, 8, 10, 12:* vincristine 1 mg/m^2 IV on day 1, prednisone 40 mg/m^2/d PO on days 1-5, 6-mercaptopurine 75 mg/m^2/d PO on days 8-28, methotrexate 15 mg/m^2/d PO/IM on days 8, 15 and 22, idarubicin 10 mg/m^2 IV on day 1 (cycles 4, 8 and 12 only). **<u>M-POS/HR and VHR patients excluded from SCT: 3rd option Maintenance (24 4-week cycles)</u>** • *Maintenance cycles 1, 3, 5, 7, 9, 11:* cytarabine 300 mg/m^2 IV on day 1, cyclophosphamide 100 mg/m^2/d PO on days 1-4, 6-mercaptopurine 75 mg/m^2/d PO on days 8-28, methotrexate 15 mg/m^2/d PO/IM on days 8, 15 and 22. • *Maintenance cycles 2, 4, 6, 8, 10, 12:* vincristine 1 mg/m^2 IV on day 1, prednisone 40 mg/m^2/d .PO on days 1-5, 6-mercaptopurine 75 mg/m^2/d PO on days 8-28, methotrexate 15 mg/m^2/d PO/IM on days 8, 15 and 22, idarubicin 10 mg/m^2 IV on day 1 (cycles 4, 8 and 12 only). • *Cycles 13-24:* 6-mercaptopurine 75 mg/m^2/d PO on days 1-28, methotrexate 15 mg/m^2/d PO/IM on days 1, 8, 15 and 22. <u>Variations for Ph/BCR-ABL+ ALL</u>: • *Maintenance cycles 1, 3, 5, 7, 9, 11:* imatinib 400 mgb/d PO on days 1-28, 6-mercaptopurine and methotrexate on days 1-14, cytarabine and cyclophosphamide omitted. • *Maintenance cycles 2, 4, 6, 8, 10, 12*: imatinib 400 mg/bd PO on days 1-28, 6-mercaptopurine on days 8-14, methotrexate on day 8. • *Maintenance cycles 13-24+* : imatinib 400 mg/bd PO on days 1-28, 6-mercaptopurine 75 mg/m^2/d PO on days 1-14, methotrexate 15 mg/m^2/d PO/IM on days 1 and 8. After cycle 24: imatinib 400 mg/bd PO until relapse.

C) **Neurotoxicity details of CNS prophylaxis trial (according to CTC grading).**

	ITT arm							ITD arm					
Neurotoxicity	C1	C2	C 4	C6	C8	Maint		C1	C2	C4	C6	C8	Maint
Grade 1, no. (%)													
Patients	5	1	-	-	1	1		8	2	4	1	1	-
Episodes	7	1			1	1		9	4	6	1	1	-
Arachnoiditis	1	-	-	-	-	-		-	-	-	-	-	-
Dizziness	-	-	-	-	-	1		1	-	1	-	-	-
Headache/pain	6	1	-	-	1	-		7	4	3	1	1	
Neuropathy-sensory	-	-	-	-	-	-		-	-	2	-	-	-
Visual	-	-	-	-	-	-		1	-	-	-	-	-
Grade 2, no. (%)													
Patients	4	2	4	3	1	3		12	9	8	3	4	-
Episodes	5	3	4	7	4	8		17	10	8	3	6	
Arachnoiditis	-	-	-	-	-	-		1	1	-	-	-	-
Consciousness	-	-	-	-	-	-		-	-	-	-	1	-
Dizziness	-	-	1	2	3	1		-	-	-	-	1	-
Extrapyramidal	-	-	-	-	-	-		-	-	-	-	1	-
Headache/pain	1	3	3	4	1	5		6	7	6	2	1	-
Neuropathy-motor	2	-	-	-	-	-		2	-	1	-	1	-
Neuropathy-sensory	1	-	-	-	-	-		2	-	1	1	1	-
Seizure	-	-	-	1	-	-		2	-	-	-	-	-
Syncope	-	-	-	-	-	-		2	1	-	-	-	-
Visual	-	-	-	-	-	-		1		-	-	-	-
Other	1	-	-	-	-	2		1	1	-	-	-	-
Grade 3, no. (%)													
Patients	2	-	-	-	-	-		11	2	1	1	2	-
Episodes	2	-	-	-	-	-		18	2	1	1	4	-
Arachnoiditis	-	-	-	-	-	-		3	-	-	-	-	-
Consciousness	-	-	-	-	-	-		2	-	-	-	-	-
Headache/pain	-	-	-	-	-	-		6	1		1	1	-
Neuropathy-cranial	-	-	-	-	-	-		-	-	-	-	1	-
Neuropathy-motor	-	-	-	-	-	-		2	-	-	-	-	-
Neuropathy-sensory	-	-	-	-	-	-		-	-	1	-	-	-
Seizure	1	-	-	-	-	-		2	-	-	-	-	-
Syncope	1	-	-	-	-	-		2	-	-	-	-	-
Visual	-	-	-	-	-	-		1	-	-	-	-	-
Other	-	-	-	-	-	-			1	-	-	2	-
Grade 4, no. (%)													
Patients	1	-	-	-	-	-		3	1	-	1	-	-
Episodes	1	-	-	-	-	-		5	1	-	1	-	-
Consciousness	-	-	-	-	-	-		2	-	-	-	-	-
Dizziness	-	-	-	-	-	-		1	-	-	-	-	-
Headache/pain	-	-	-	-	-	-		1	-	-	1	-	-

Neuropathy-motor	-	-	-	-	-	-		-	1	-	-	-	-
Visual	1	-	-	-	-	-		-	-	-	-	-	-
Other	-	-	-	-	-	-		1	-	-	-	-	-