

Group for Research on Adult Acute Lymphoblastic Leukemia
GRAALL Intergroup (LALA-GOELAMS-SAKK)

Protocol GRAALL 02/2005

**A Randomized Multicenter Phase III Study to Compare the Efficacy
of HyperC to Standard Induction and Late Intensification
in Younger Adults with *de novo* Philadelphia Chromosome-negative
Acute Lymphoblastic Leukemia (ALL).**

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PROTOCOL SYNOPSIS

Title	A Randomized Multicenter Phase III Study to Compare the Efficacy of HyperC to Standard Induction and Late Intensification in Younger Adults with <i>de novo</i> Philadelphia Chromosome-negative Acute lymphoblastic leukemia (Ph1-negative ALL).
Study phase	Phase III
Primary objective	To compare the event-free survival (EFS) and overall outcome of adult patients with <i>de novo</i> Ph1-negative ALL treated by HyperC versus standard induction and late intensification.
Secondary objectives	<p>To assess and compare the impact of both treatment arms on :</p> <ol style="list-style-type: none"> 1. Induction toxicity profile. 2. Hematological complete remission (HCR) rate and number of course needed to reach HCR. 3. Early death rate. 4. Death in first HCR rate. 5. Incidence of hematological relapse. 6. Disease-free survival. 7. Overall survival. <p>These comparisons will be performed in the whole population of patients randomized without and then with censoring transplanted patients at the time of allogeneic stem cell transplantation (SCT).</p> <p>They will also be performed in the two subgroups defined according to the risk classification exposed below.</p>
Risk groups	<p>Two risk subgroups (high-risk or HR versus standard-risk or SR) are defined according to baseline ALL characteristics as well as time-dependent criteria based on the early response to therapy.</p> <p>The HR group is defined by the presence of at least one of the following criteria :</p> <ul style="list-style-type: none"> ○ WBC > 30.000/mm³ if B-lineage ALL. ○ CNS involvement (clinical and/or morphological). ○ ProB-ALL (B1 for EGIL) ○ t(4;11) and/or <i>MLL-AF4</i>+ B-lineage ALL. ○ t(1;19) and/or <i>E2A-PBX1</i>+ B-lineage ALL. ○ <i>SIL-TAL</i> or <i>HOX11L2</i> T-ALL ○ Haploid or near-triploid ALL (DNA index). ○ Corticoreistance after the prophase. ○ Chemoresistance after the first week of chemotherapy. ○ Need of a second induction course (salvage) for HCR. ○ IgH-TCR or fusion transcript MRD ≥ 10⁻² after induction (MRD-1) ○ IgH-TCR or fusion transcript MRD ≥ 10⁻² after 3 consolidation blocks (MRD-2) <p>Only HR patients will be eligible for allogeneic SCT in first HCR if appropriate age and matched donor.</p>

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<p>Induction groups</p>	<p>All adult patients aged 15-59 years with <i>de novo</i> Ph1-negative ALL will be eligible for the study. All adult patients with <i>de novo</i> ALL will be prospectively registered and enrolled in the GRAALL-2005 protocol prephase comprising 1 mg/kg/d oral prednisone (PDN) and one intrathecal injection of methotrexate (IT-MTX). The diagnosis of Ph1-negative ALL will have to be confirmed during this 7-day prephase period (Day -7 to Day -1) by standard cytogenetics or FISH and <i>BCR-ABL</i> PCR. At the end of the prephase (Day 1), those with Ph1-negative ALL will be enrolled in a common first part of induction course and randomized at Day 1 of this course between 2 further treatment arms (standard or HyperC) :</p> <p>Common first part of induction (Day 1 to Day 14) :</p> <p>VCR, DNR, CPM, PDN,L-Aspa;Triple IT</p> <p>Arm A (standard induction – from Day 15) :</p> <p>VCR, DNR, CPM, L-Aspa, G-CSF (from D18)</p> <p>Arm B (HyperC induction – from Day 15) :</p> <p>VCR, DNR, CPM, L-Aspa, G-CSF (from D18)</p> <p style="text-align: right;">↑ Response Assessment (MDR-1) ↑ Response Assessment (MDR-1)</p> <p>In both arms :</p> <p>A first peripheral blood (PB) and marrow assessment of response will be done at Day 36 of the induction course (standard PB and marrow criteria).</p> <p><i>In patients in first HCR after induction, a first assessment of BCR-ABL minimal residual disease (MRD) will be performed at this time (<u>MRD-1 point</u>).</i></p>
<p>Salvage course</p>	<p>Patients not achieving HCR after induction will receive the following salvage course combining idarubicin (IDA) and high doses of cytarabine (HD-AraC)</p>
<p>Consolidation blocks</p>	<p>Patients not achieving HCR after induction + salvage will go out of the study. Patients achieving HCR after induction +/- salvage will then all receive two series of 3 consecutive blocks of consolidation (namely 1 HD-AraC block, 1 HD-MTX block, and 1 HD-CPM block), as follows :</p> <p>These three blocks will be administered at Day 1, Day 15, and Day 29 strictly, without waiting for the myeloid recovery between two consecutive blocks of each series. However, recovery from myelosuppression must occur between the two series.</p> <p><i>In patients in persistent first HCR, a second assessment of BCR-ABL MRD (<u>MRD-2 point</u>) will be performed after the first three blocks.</i></p>
<p>Patients eligible for SCT</p>	<p>Allogeneic SCT in first HCR will be offered to patients with HR-ALL and a matched familial related donor (MFR) until the age of 55 years or to those with HR-ALL and a matched unrelated donor (MUD) until the age of 45 years. SCT has to be done either after the first or the second series of consolidation blocks, depending on the time a donor will be identified. Before SCT, patients may receive 1 or 2 optional interphase courses of</p>

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	HD-MTX and L-Aspa .
SCT	Standard TBI-CPM conditioning regimen followed by standard CsA-MTX graft-versus-host disease prophylaxis.
Late intensification	<p>After the consolidation phase (2 x 3 blocks), all patients in persistent HCR and not allocated to receive allogeneic SCT in first HCR (those with SR-ALL or those with HR-ALL but no donor) will receive a late intensification comprising two consecutive parts.</p> <p>First part :</p> <p>Basically, the first part of the late intensification is a repetition of the induction course the patient had previously receive, omitting the prephase. Patients randomized in Arm A will receive a standard late intensification. Those randomized in Arm B will receive a HyperC late intensification. This first part will include 2 additional triple IT (#5 and #6).</p> <p>In patients who have reached HCR after salvage only, this first part will be entirely different and comprise IDA, HD-AraC, triple IT and G-CSF.</p> <p>Second part :</p> <p>Basically, the second part of late intensification is a repetition of 3 consolidation blocks exactly similar to the 3 blocks used in the two series of the consolidation phase. The triple IT planned with the third HD-CPM block will, however, be omitted.</p>
CNS irradiation	In addition to the first single MTX IT and the 6 triple IT administered so far, CNS prophylaxis also includes a 18-Gy CNS irradiation, performed after the second part of late intensification and before the onset of the maintenance phase simultaneously with 6-mercaptopurine (6-MP) oral administration.
Maintenance	<p>Two years of 6-MP and MTX</p> <p>Monthly reinductions during the first 12 months only, comprising VCR and PDN.</p> <p>In the event of unexpected prolonged cytopenias or safety concerns, adapted dosages should be considered (refer to Appendix 6).</p>
Study design	Prospective, randomized, multicenter, open Phase III.
Study size	810 randomized patients (405 patients in each arm)
Period of enrolment	Given an annual recruitment rate of 220 patients aged 15-59 years with <i>de novo</i> ALL per year and an incidence of Ph1-negative ALL of 75%, the total study duration is anticipated to be 5 years.

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Inclusion criteria	<ol style="list-style-type: none"> 1. Patient aged 15 to 59 years with previously untreated <i>de novo</i> Ph1-negative ALL (with the exception of the steroid prephase including one intrathecal injection of MTX) with at least 20% leukemic marrow blasts. 2. After voluntary signed informed consent.
Non-inclusion criteria	<ol style="list-style-type: none"> 1. ALL-L3 in the French-American-British classification. 2. Prior myeloproliferative syndrome, including Ph1-positive CML. 3. ECOG Performance Status Score \geq 3. 4. Creatinine level more than 2x's the upper limit of the normal range (ULN) at the laboratory where the analysis was performed, except in ALL-related. 5. Total serum bilirubin more than 2x's the ULN at the laboratory where the analysis was performed, except if ALL-related. 6. AST (SGOT) or ALT (SGPT) more than 5x's the ULN at the laboratory where the analysis was performed, except if ALL-related. 7. Positive pregnancy test (contraceptive precautions are to be used throughout the study in both sexes). 8. Positive serum test for HIV or HTLV-1 9. NYHA Grade 3/4 cardiac disease. 10. Active severe infection. 11. Psychiatric disease or an history of non-compliance to medical regimens or patients considered potentially unreliable.
Primary endpoint	Event-free survival (EFS).
Secondary endpoints	<p>Induction course :</p> <ul style="list-style-type: none"> ▪ Severe hematological and non-hematological toxicity. ▪ Early death rate. ▪ HCR rate. <p>Outcome :</p> <ul style="list-style-type: none"> ▪ Rate of death in first HCR. ▪ Incidence of hematological relapse. ▪ Disease-free survival of HCR patients. ▪ Overall survival. ▪ Overall survival in patients who may receive SCT in first HCR.

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Study procedures	<p>All patient aged 15-59 years with <i>de novo</i> Ph1-negative ALL are to be informed about the study procedures of this prospective study and randomized at Day 14 between both induction arms unless they refuse to participate in the study or present non-inclusion criteria.</p> <p>Randomization between both arms will be stratified on centers, age (15-45, 46-55, 56-59), and ALL lineage (B versus T).</p>
Statistical considerations	<p>Based on historical experiences, an estimated 5-year EFS of 35% is anticipated in the standard induction arm (Arm A).</p> <p>The objective is to reach an estimated 5-year EFS of 45% in the HyperC arm (Arm B).</p> <p>With an alpha-risk of 0.05 and a beta-risk of 0.15, the number of randomized patients needed for the study is 810 (405 patients in each arm). Statistical analysis will be based on an intent-to-treat principle and use the log-rank test.</p>