



# PATIENT INFORMATION SHEET

Version No: 03 Date (13/12/2004)

## I. Study Information

### Protocol Title:

**Singapore-Malaysia Acute Lymphoblastic Leukaemia (ALL) Treatment Protocol**

### Principal Investigator & Contact Details:

Dr Allen Yeoh Eng Juh  
The Children's Medical Institute  
National University Hospital  
5 Lower Kent Ridge Road  
Singapore 119704  
Tel : 65-67724420

## II. Purpose of the Research Study

You are being invited to participate in a research study.

Before you take part in this research study, the study must be explained to you and you must be given the chance to ask questions. Please read carefully the information provided here and, if you agree to participate, please sign the informed consent form (page 5). You will be given a copy of this document to take home with you.

You are being invited because your child has been diagnosed to have acute lymphoblastic leukaemia (ALL).

This study is being performed in order to find out

1. Whether tailoring the intensity of therapy to the risk of relapse will help improve the risk-benefit ratio of treatment.
2. New markers for diagnosis and prediction of outcome for childhood ALL
3. The frequency of various metabolizing enzymes in the Singaporean population that has impact on the drugs used in the treatment of ALL.

This study will recruit 200 subjects from 4 institutions in Singapore and Malaysia over a period of 4 years from Jan 2003 to Dec 2006.

## III. What procedures will be followed in this study?

There is *no* randomization in this study.

If you agree to take part in this study, you will be asked to provide consent for the study. Your child will undergo treatment according to the risk group assigned based on his response to therapy. Your participation in the study will last 2 years of therapy with subsequent follow-up for 4 years. The prescribed therapy for the protocol for about 2 years. You will need to visit the doctor's office two times a week in the beginning of therapy and subsequently fortnightly during the maintenance therapy of the study.

If you agree to take part in this study, the following will be carried out for your child:

1. Full blood count twice a week during the first month of therapy. This is followed by weekly full blood count for the first year of therapy.
2. Bone marrow tests will be carried out at diagnosis, day 8, day 15, day 33 and week 12 of therapy to allow us to measure the response to therapy and predict the risk of relapse.
3. Blood tests will be taken from your child, your spouse and yourself to determine the pharmacogenetic profiles at diagnosis.

In total, 4 teaspoons of blood will be taken as part of this study.

There are no investigational drugs in this study. All the drugs used are standard established therapy for childhood ALL for the last 30 years.

#### **IV. Your Responsibilities in This Study**

If you agree to participate in this study, you should follow the advice given to you by the study team. You should be prepared to visit the hospital twice a week and whenever necessary and undergo all the procedures that are outlined above.

#### **V. What Is Not Standard Care or Experimental in This Study**

Our treatment of childhood ALL has been very successful with 80% of children cured. Unfortunately, treatment of childhood ALL using chemotherapy is associated with short-term and long-term side-effects. To obtain the best risk-benefit ratio of therapy, we need to carefully tailor the therapy according to the patient's risk of relapse.

We can accurately define the patients' risk of relapse early during therapy.

1. A standard risk group of patient who are at low risk of relapse (<15%),
2. an intermediate risk group with ~25% chance of relapse and
3. a high-risk group with >50% risk of relapse.

We hope to reduce the dose of one chemotherapy drug group which may have long-term side-effects on the heart in the standard risk patients who have low risk of relapse without affecting the outcome. For the high-risk patients, we hope to further intensify therapy to avoid relapse. Relapsed ALL is both very difficult to treat and has poor outcome.

Your child will be assigned to one of 3 risk groups depending on his risk of relapse as predicted by his early response to therapy and certain special laboratory tests. Standard risk patients which comprise of about 40% of the patients and has a high chance of cure, will receive a slightly reduced intensity of therapy to reduce long-term side-effects. The mild reduction in therapy in the Standard Risk group has not been shown to have adverse impact on overall outcome. This has potential benefits of less short and long-term toxicities.

For High Risk group, who has significantly lower chance of cure, further intensification of therapy is implemented. The further intensification for the high risk group has been proven to be effective in a large cohort of patients in USA and Europe. By putting the best therapy and even bone marrow transplantation in certain patients upfront, we hope that the best chance of cure if given from the beginning of therapy.

For Intermediate Risk patients, the total dose of therapy is given is similar to our previous protocol, except that the scheduling is changed to decrease toxicity. This change in scheduling will allow us to administer the chemotherapy safely and effectively.

This study is being conducted because tailoring of therapy as defined above is not yet proven to

be a standard treatment in children with ALL. We hope that your participation will help us to determine whether tailoring therapy based on the risk of relapse is equal or superior to existing therapy based on conventional prognostic markers of age and WBC count at diagnosis.

No placebo or randomization of the study will be carried out.

Although tailoring of therapy may be part of standard medical care, in this study this/these procedure(s) are only being performed for the purposes of the research, and are not part of your routine care.

## **VI. Possible Risks and Side Effects**

The therapy used in this study is a well-established protocol used by thousands of patients in the world including Singapore, Europe and American for up to the last 30 years. This is one of the proven highly successful therapy.

As with any therapy, there are complications expected. However, ALL is a cancer and can kill without proper chemotherapy. As such, great care has been put in to ensure that your child receive the best therapy that provide him the best chance for cure.

Infections and bleeding are common complications of chemotherapy as part of cancer treatment. You will be counseled on what to do during these complications. You may contact our nurses in the Paediatric Inpatient Cancer Centre at 65-67725478/9 if any problems arise.

Allergic reactions can occur with any drug. Common symptoms may include: rash, itching etc.

Rarely, a severe and possibly life-threatening allergic reaction can occur. Symptoms of a severe reaction include: swelling of the face, difficulty breathing, a sudden drop in blood pressure that may cause dizziness. If you have any of these symptoms, call your doctor at once.

If you experience any new symptoms, you should contact your doctor or the Principal Investigator as soon as possible.

Obtaining blood and bone marrow can cause pain, bleeding, bruising, or swelling at the site of the needle stick. Fainting sometimes occurs and infection rarely occurs.

Any blood or tissue specimens obtained during the course of this study will be stored and analysed only for the purposes of this study. Excess tissues that are not used for this study will be stored in our Cell Bank and may be used for future studies that may benefit the treatment of future children with ALL.

In addition, as you cannot give any other medication to treat your child's ALL while he or she is receiving therapy, there is a possibility your condition may worsen. If in doubt, please discuss with your doctor who is treating your child.

## **VII. Important Information for Women Subjects**

Not applicable. This study is applicable to children below the age of 18 years.

## **VIII. Alternatives to Participation**

If you choose not to take part in this study, the alternative is to have what is considered standard care for your condition. In our institution this would be treatment using the older treatment regimens like the NUH ALL protocol which has 68% cure rate. That older protocol (NUH ALL II) has the following potential benefits:

1. cheaper upfront cost as the drugs and doses used are significantly lower than our current therapy.

2. less upfront side-effects of fever and needing blood product support.

and the following potential risks:

3. Higher relapse rate as this new protocol has superior approximately 80% cure
4. Higher total cost of therapy as relapse therapy is much more expensive and poorer outcome. This may involve bone marrow transplantation.

## **IX. Possible Benefits from Participating in the Study**

If you participate in this trial you may reasonably expect to benefit from the Singapore-Malaysia ALL 2003 study in the following way:

1. Improved prediction and accuracy of relapse. This involves new proven laboratory techniques of oncogene fusion screening and minimal residual disease analyses which can help improve our accuracy of prediction of the patient's eventual risk of relapse.
2. Detection of mutations of certain metabolizing enzymes like Thiopurine MethylTransferase (TPMT) enzyme which may be associated with increased toxicity when the standard dose of therapy of certain chemotherapy drugs are used.

## **X. Costs & Payments if Participating in the Study**

If you take part in this study, the following will be performed at no charge to you:

1. Oncogene fusion screening for the common translocations in ALL
2. Minimal residual disease detection assay
3. Pharmacogenetic analyses for TPMT

If you take part in this study, you will have to pay for the following tests which are standard in management of your child with ALL:

1. FBC, and chemistries
2. Bone marrow aspirates
3. CSF analyses for leukaemia in the brain.

No monetary remuneration will be given.

## **XI. Voluntary Participation**

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the Principal Investigator or your treating physician.

Your doctor, the Investigator and/or the Sponsor of this study may stop your participation in the study at any time if they decide that it is in your best interests. They may also do this if you do not follow instructions required to complete the study adequately. If you have other medical problems or side effects, the doctor and/or nurse will decide if you may continue in the research study.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you or your legal representative will be informed in a timely manner by the Principal Investigator or his/her representative.

## **XII. Compensation for Injury**

If you follow the directions of the doctors in charge of this study and you are physically injured

due to the trial substance or procedure properly given under the plan for this study, the *NHG* will pay the medical expenses for the treatment of that injury.

Payment for management of the normally expected consequences of your treatment, will not be provided by the *NHG*. By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

### **XIII. Who To Contact if You Have Questions**

If you have questions about this research study and your rights, you may contact the Principal Investigator,

Dr Allen Yeoh Eng Juh  
The Children's Medical Institute  
National University Hospital  
5 Lower Kent Ridge Road  
Singapore 119704  
Tel : 65-67724420

In case of any injuries during the course of this study, you may contact the Principal Investigator,

Dr Allen Yeoh Eng Juh  
The Children's Medical Institute  
National University Hospital  
5 Lower Kent Ridge Road  
Singapore 119704  
Tel : 65-67724420

If you want an independent opinion of your rights as a research subject you may contact the *NHG* Domain-Specific Research Board Secretariat (Attn: Sujatha Sridhar) at 6471-3266.

### **XIV. Confidentiality of Study and Medical Records**

Information collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available.

However, the National Medical Research Council, Singapore Cancer Syndicate, Regulatory Agencies and *NHG*- Domain Specific Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you or your legal representative are authorizing such access to your study and medical records.

Data collected and entered into the Case Report Forms are the property of (*Institution or Company*). In the event of any publication regarding this study, your identity will remain confidential.

# Patient Informed Consent Form

Version: *Number 02* Date: 17/11/2004

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**Principal Investigator & Contact Details:**

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I voluntarily consent to take part in this research study.

I have fully discussed and understood the purpose and procedures of this study.

This study has been explained to me in \_\_\_\_\_ (language)

on \_\_\_\_\_ (date) by \_\_\_\_\_ (name of translator).

I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to the best of my doctor's ability.

I agree / do not agree [circle selected option] to the use of the data for future studies.

I agree / do not agree [circle selected option] to the use of my blood/tissue samples for future studies.

\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Witness

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

**Investigator Statement**

I, the undersigned, certify to the best of my knowledge that the patient signing this informed consent form had the study fully explained and clearly understands the nature, risks and benefits of her participation in the study.

\_\_\_\_\_  
Name of Investigator

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date