(To be printed on hospital/institution headed paper)

PATIENT INFORMATION SHEET

Patient Trial Number: RCM | | | |

Version Number 7.1
Date: 01.09.2010

Trial title: A Phase II Single Arm Study of the use of CODOX-M/IVAC with Rituximab (R-CODOX-M/IVAC) in the treatment of patients with Diffuse Large B-Cell Lymphoma (DLBCL) or Burkitt's Lymphoma (BL) of International Prognostic Index (IPI) High or High-Intermediate Risk
Short title: R-CODOX-M/IVAC

REC Reference: 05/Q0201/81

You have been invited to take part in a research study. Before you decide if you would like to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP, if you wish.

If you decide to enter the study your GP will be made aware of your participation in the study. If you do not want your GP to be informed of your involvement in the trial, then you will be unable to participate. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

You have a condition called non-Hodgkin's lymphoma. In particular, you have a subtype of non-Hodgkin's lymphoma called diffuse large B cell non-Hodgkin's lymphoma or Burkitt's lymphoma. This is a cancer of the lymphatic system, which extends throughout the body. This means the cancer may be present in more than one part of your body. This is an aggressive cancer but is curable with intensive chemotherapy. We are developing a new intensive treatment programme for patients who have disease like yours. This programme involves a combination of standard chemotherapy drugs (CODOX-M/IVAC) and a drug called rituximab.

CODOX-M/IVAC is a combination of chemotherapy drugs that are active in lymphoma. It consists of the following medicines: cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide and ifosfamide. Rituximab is a form of antibody whose action is directed against a protein present on the surface of lymphoma cells. Rituximab has been shown in previous clinical trials to be effective in diffuse large B-cell lymphoma. We would like to find out whether giving CODOX-M/IVAC with rituximab, which is a more intensive treatment will induce a better response rate and increase your lifespan.

If you agree to take part, you will be treated with 2 cycles of CODOX-M/IVAC chemotherapy and 8 doses of rituximab. In total, 150 patients like you will take part in the study.

Why have I been chosen?

You have a new diagnosis of aggressive diffuse large B-cell lymphoma or Burkitt's lymphoma and therefore you are suitable for this study. We are asking whether you would like to participate in this study.

Do I have to take part?

Your participation in this trial is entirely voluntary. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. A decision to withdraw or a decision not to take part will not affect the standard of the care you receive.

What will happen to me during the study?

If you are willing to participate in the clinical trial, your doctor will assess you to ensure you are suitable to take part. This would include full medical details, physical examination, blood tests and tumour assessment (CT scan, chest X-ray and bone marrow biopsy). Blood samples will be taken before and during every treatment. The amount of blood taken at each occasion will not exceed a tablespoon in volume. **All these investigations are done routinely whether you decide to participate in the study or not.**

You will receive chemotherapy drugs (CODOX-M/IVAC) and rituximab. This treatment is quite intensive and all patients will require a period of time in hospital for each course of chemotherapy, i.e. 4 admissions, for the administration of the 2 courses of CODOX-M and 2 courses of IVAC. In total it will take about 16 weeks to give this treatment. It is likely you will be in hospital for a 2-week period every 2 weeks, i.e. 2 weeks in hospital, 2 weeks out of hospital for 16 weeks. On rare occasions continuous admission for 2-3 months will be required.

The treatment you receive will temporarily impair the ability of your bone marrow to produce blood cells and, depending upon your clinical condition, you may require blood transfusions, intravenous antibiotics or platelet transfusions, all given directly into a vein in you arm. The chemotherapy drugs cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and rituximab are also given into a vein in your arm. In addition you will need to receive intrathecal treatment (that is chemotherapy treatment given via a needle into the fluid around the spine). This will occur on a minimum of 8 occasions if you receive full protocol treatment or on a maximum of 12 occasions if there is evidence of lymphoma in the brain or central nervous system or you have been diagnosed with Burkitt's lymphoma. This will be required as treatment with intravenous chemotherapy is ineffective at controlling lymphoma in the brain or central nervous system.

You will also receive an injection called granulocyte colony stimulating factor (G-CSF) to boost your white blood cells to help us give the treatment on time. This is given

underneath your skin either on your stomach, on your arm or on your thigh during every cycle.

We shall repeat your CT scan at the end of treatment to assess the response of your lymphoma and at 4 months and 1 year after finishing treatment. At the end of treatment, a bone marrow biopsy will also be repeated (if involved at diagnosis). You will then be seen regularly in the clinic. Clinic visits with physical examination will occur at 1-4, 6, 8 10, 12, 15, 18, 21, 24, 28, 32, 36 months after completion of R-CODOX-M/IVAC, then 6 monthly for 1 year then annually for life.

What will happen to any samples I give?

Blood samples taken for the study will be collected and processed in exactly the same way as other samples taken in your hospital and will be destroyed after analysis. Your tissue biopsy will be reviewed by a pathologist in another hospital to confirm the diagnosis. Additional tests for biological risk factors will be performed, although these results will not alter the treatment you receive. In addition, and with your permission, a small fragment of the lymphoma tissue that was taken to make your diagnosis will be stored. This may be used in future research studies. This material will be linked to the data collected during your participation in the study through your unique trial number. No other personal data will be held. We shall seek a separate ethics approval before any use of this material for future studies. This tissue is needed for research to improve the treatment of lymphoma in the future. The donation of this tissue sample is entirely voluntary. You can decide not to consent to this part of the trial and still be eligible for the remainder of the trial.

Payment:

You will not receive any payment or reimbursement of expenses for taking part in this study.

What do I have to do?

There are no particular lifestyle restrictions necessary. CODOX-M/IVAC chemotherapy and rituximab can affect egg and sperm production and therefore effective contraception should be used during and for 12 months after the last dose of treatment.

Are there any side effects associated with these treatments?

CODOX-M/IVAC chemotherapy is extremely effective, but can be associated with quite severe, mainly short-term, side effects. For this reason you will be required to be an inpatient during and after the administration of chemotherapy. There are both general side effects of chemotherapy and those specifically related to R-CODOX-M/IVAC as listed below.

After chemotherapy, possible general side-effects include:

1) Sore mouth – you will be given a mouthwash in an attempt to prevent this.
2) Diarrhoea – this is usually mild, but if it is persistent tablets will be provided to help relieve this.
3) Nausea and vomiting – this is usually controlled with anti-sickness drugs.

4) Lowering of the blood count - this usually does not cause symptoms but it does increase the risk of infection, bruising and bleeding. This is one of the reasons why you need to be in hospital and sometimes blood and platelet transfusions are necessary. It is likely you will require intravenous antibiotics
5) Loss of head and body hair – the hair usually grows back shortly after the chemotherapy is stopped.
6) Numbness or tingling sensation in hands and feet only. This is usually temporary but occasionally can be permanent.
7) Damage to heart, lungs, liver and kidneys can occur with the chemotherapy. This will be carefully monitored during treatment and measures initiated as appropriate.

Specific possible side effects of the drugs in CODOX-M/IVAC include:

Cyclophosphamide, Ifosfamide – bleeding from the bladder
Doxorubicin - palpitations, weakening of the heart musculature
Vincristine – nerve damage including tingling in hands and feet, constipation
Etoposide – liver damage if impaired liver function

There is also an increased risk of developing thromboembolism (blood clots) due to both the lymphoma and the chemotherapy. You should contact your doctor promptly if you develop swollen or painful legs (especially if only in one leg) or if you develop shortness of breath, chest pain or cough up blood. If you did develop a blood clot, this would be treated with injections to thin your blood.

After rituximab:
Mild and temporary side effects often occur during the first treatment. These include fever, chills, headache, tiredness, aching muscles and joints, itching, redness of skin, nausea and mild drop in blood pressure. Most of these disappear upon temporary slowing or discontinuation of the treatment or after the administration of paracetamol and/or anti-allergic medication.
Serious effects have occurred 1–2 hours after infusion of rituximab due to a severe allergic reaction characterised by marked shortness of breath. You are therefore monitored very closely during the infusion and a slower rate of infusion given if necessary.

The Medicines and Healthcare products Regulatory Agency (MHRA), the government body that checks the safety of drugs, has warned that a very small number of people taking rituximab for non-Hodgkin's lymphoma developed a dangerous brain infection. Some of these people died. But doctors don't know for sure if rituximab caused the illness. In some cases, the infection happened more than one year after people stopped taking rituximab

GCSF:
You may experience some pain in your bones as the GCSF stimulates the bone marrow.

If any of these symptoms are severe, then the dose of your chemotherapy will be reduced. In exceptional circumstances, your doctor may decide to permanently discontinue treatment and this will be discussed with you.

CT Scans:

CT scans involve a possible risk as they involve exposure to radiation. However, the doses are very small when compared to the dose of radiation received as part of radiation treatment, for example. Nevertheless, the amount of scans you have will be kept to a minimum. A CT scan is equivalent to up to 13 years background radiation. A total 2 CT scans will be carried out on this study, some of which would be part of standard practice even if you were not on a trial. This level of exposure is unlikely to lead to a significant health risk for you.

Just as anybody else receiving chemotherapy, you will need to take adequate contraceptive measures while receiving treatment. This is because during treatment and for one year after chemotherapy, your sperm or eggs may not be formed normally, if they are produced at all, treatment might also harm an unborn child. Therefore, if there is a chance that you or your partner could become pregnant you must agree to use a reliable form of contraception during the trial and for at least 12 months after the last trial treatment. Reliable forms of contraception are oral, injected, or implanted hormonal methods and condom, intra-uterine device (IUD) or intra-uterine system (IUS) and condom, diaphragm or cervical/vault caps with spermicide and condom. You should share this information with your partner as birth defects can occur in any pregnancies during this period.

If you or your partner become pregnant during the study or for 12 months after the last trial treatment, we would ask you to tell your study doctor immediately

This treatment will make most patients infertile. All males and females over 30 years are likely to become infertile. Prior to commencing chemotherapy arrangements can be made for sperm storage. Women younger than 30 years may retain their fertility. It is though likely they will experience an earlier menopause by 5-10 years.

What are the possible benefits of taking part?

We hope that the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to improve the future treatment of patients like you with diffuse large B cell non-Hodgkin's lymphoma or Burkitt's lymphoma.

What if something goes wrong?

Every care will be taken in the course of this clinical trial. However if you are harmed by taking part, University College London (UCL), as sponsor, will provide non-negligent compensation (i.e. compensation without the need to prove that there has been negligence). If, however, you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you should ask to speak to the researchers, who will do their best to answer your questions (*contact number*). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital and from the Department of Health website:
http://www.dh.gov.uk/en/Managingyourorganisation/Legalandcontractual/Complaintspolicy/NHScomplaintsprocedure/DH_4080897

Please ask your study doctor if you would like more information about this.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your study doctor will make arrangements for your care to continue. If you decided to continue in the study you will be asked to sign an updated consent form.

On receiving new information, your doctor might consider it to be in your best interests to withdraw from the study. He/she will explain the reasons and arrange for your care to continue.

Will information about me in this study be kept confidential?

If you consent to take part in the research your medical records will not be seen outside the Cancer Centre and will only be used by the clinical staff involved in the research programme, in addition to those looking after your general treatments. The details of your treatment and response will be sent to the Cancer Research UK & University College London Cancer Trials Centre (UCL CTC) where statistical analysis will be performed. The information we send to the Trial Centre will be anonymised so that the trials staff, statisticians, scientists do not have direct access to your personal details, but will contain information or codes that allow you to be identified. Staff working on the trial at UCL CTC will have access to your medical records at the hospital for the purposes of monitoring the trial. We will also use information from the NHS Information Centre to follow your progress if this is not available from your hospital or General Practitioner. **The data management of this study will comply with the Data Protection Act 1998.**

Who is sponsoring and organising the research?

This study is organised on behalf of the National Cancer Research Institute and is co-ordinated by UCL CTC.

What will happen to the results of the study?

Results will be analysed by UCL CTC. They will be presented at national and international haematological and oncological meetings and published in associated journals. Results will be published collectively so it will not be possible to identify individuals.

What if I do not wish to take part or change my mind?

The study is voluntary so that you should not feel under any pressure to enter. If you decide to take part you are free to withdraw at any time. In either case, you do not have to give a reason for your decision and this will not prejudice your future medical care. If you decide not to participate in the study, then your doctor will discuss other options with you.

Who has reviewed the study?

This study has been reviewed and approved by the Hertfordshire Research Ethics Committee.

Thank you

Thank you for considering taking part and taking the time to read this sheet.

Contact for further information

CancerBACKUP, who are an independent organisation provide support and counselling to help people live with cancer. They can be contacted at:

http://www.cancerbackup.org.uk/Contactus/Contactdetails

Cancerhelp (Cancer Research UK) who provide all aspects of information for people with cancer. Their contact details are:

Tel: 020 7061 8355

Free phone: 0808 800 1234

Or visit their website at http://www.cancerhelp.org.uk

Useful contacts:

Local Contacts:

Your doctor ..... Tel: .....

Your nurse ..... Tel: .....

In the event of out of hours medical emergencies you should contact:

Name: .....

Contact Number: .....