19.0 RECIPIENT MODEL CONSENT FORM

A Phase II Study of Reduced-Intensity Allogeneic Transplant for Patients with High-Risk Chronic Lymphocytic Leukemia

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to participate in this trial because you have been diagnosed with chronic lymphocytic leukemia (CLL) that either is considered to have high risk factors or has returned despite previous therapy. Patients considered to have CLL with high-risk features at diagnosis may not respond to standard chemotherapy.

Why is this study being done?

The purpose of this study is to find out what effects (good and bad) this treatment has on you and your type of cancer. This research is being done to improve the outcomes of patients diagnosed with chronic lymphocytic leukemia who may have high risk features or who have had their disease return after receiving chemotherapy.

There is evidence that "stem cells" donated from a sibling (that is, a brother or sister) or another compatible person can be used as part of an effective therapy for CLL. After transplant into the patient, the donor's stem cells (cells that have the ability to develop into red blood cells, white blood cells, or platelets) appear to have the ability to recognize and kill the patient's leukemia cells. This powerful reaction performed by the donor's stem cells is known as the "graft-versus-leukemia," or GVL, effect.

In the past, stem cell transplantation required high doses of chemotherapy and/or radiation in the patient immediately prior to infusion of the donor's stem cells. Success in controlling or eliminating cancer was believed to be the result of a combination of the high-dose chemotherapy/radiotherapy and the GVL effect described above. The high doses of chemotherapy and/or radiation and the serious side effects that result from it, restricted its use in young patients or patients without other significant medical problems. Recently, success has been had using lower doses of chemotherapy without radiation; the lower doses of chemotherapy have reduced and/or eliminated some of the serious side effects. When lower doses of chemotherapy without radiation are used, these types of transplants are referred to as "reduced intensity" transplants. The reduced intensity transplant in this study is considered standard, but the use of transplant early as an option for patients with high-risk features is considered experimental. The use of rituximab after the reduced intensity transplant is also considered experimental.

How Many People Will Take Part in the Study?

As many as 86 people will take part in this study. It is anticipated that approximately 39 people diagnosed with CLL with high risk features, and 39 people diagnosed with CLL whose disease has returned despite treatment with chemotherapy will be enrolled.

What will happen if I take part in this research study?

Medical Tests

The following tests must be done to make sure that you are eligible for this study. None of these tests are experimental and are all part of regular cancer care. They are routine. Depending on when you last had them, you may need to repeat some of these tests:

- Blood tests
- Physical Exam
- CT scan of your chest, abdomen, pelvis
- Pulmonary Function Tests (PFT) (a test of lung function)
- Echocardiogram or MUGA (a test of heart function)
- Hepatitis, HIV Test
- Bone marrow aspirate and biopsy
- Pregnancy test (if you are a woman of child-bearing potential)

Many of these tests will be repeated during the study. If you participate in this study, some of these tests may be done more frequently than if you were not taking part in this research study.

Treatment

The standard treatment for your disease is chemotherapy. This research study will attempt to use a different approach that will use a donor's stem cells to fight your disease. The donor's stem cells will be obtained either from a well-matched relative or from a well-matched individual unrelated to you. The chemotherapy to be given to you during the stem cell transplant is meant to weaken your immune system (including the white blood cells responsible for fighting infections) in preparation for the introduction of your donor's stem cells. The goals of this study are: 1) to replace the leukemic cells responsible for your disease with normal cells from your donor with transplant, and 2) after transplant, to use another drug, called rituximab, to help eliminate any residual or remaining CLL cells. During the transplant component of this research study, your study doctor will recommend one of two transplant chemotherapy treatments, as well as one of two treatments to prevent a specific side effect from transplantation, known as graft-versus-host disease. Graft versus host disease (GVHD) is a side effect of bone marrow or stem cell transplantation. Your donor's stem cells treat your body as "foreign" and launch an attack against it. The most common sites of attack by cells causing GVHD are the skin, liver, and gastrointestinal tract.

Transplant Chemotherapy Treatment #1

Transplant chemotherapy treatment #1 uses the drugs fludarabine, busulfan, and rituximab. The drugs will be given to you by intravenous (IV) infusion, that is through a needle in a vein in your

arm or through a "central line," a catheter (or tube) placed in the large vein under your collarbone or your neck. The day your donor's stem cells will be given to you will be known as Day 0 or the day of transplant. In the description of the treatment that follows, when a drug is given before Day 0, the day of transplant, it will be noted with a negative sign (-). For example, -7 means seven days before Day 0, the day of transplant. When a drug is given after Day 0, the day of transplant, it will be noted with a positive sign (+). For example, +7 means seven days after Day 0, the day of transplant. The first drug to be given will be rituximab. Rituximab will be given by IV infusion on four separate days one week apart. Rituximab will be given on Days -7, -1, +7, and +14 (that is, rituximab will be given seven days *before* Day 0, one day *before* Day 0, seven days *after* Day 0, and fourteen days *after* Day 0). Fludarabine will be given by IV infusion over 30 minutes each day for four (4) days. Fludarabine will be given on Day -5 through Day -2 (that is, fludarabine will be given five days *before* Day 0, the day you receive your donor's stem cells). Busulfan, another chemotherapy drug, will be given also by IV infusion for four days. Busulfan will be given on Days -5 through -2 (that is, busulfan will be given five days *before* Day 0, the day you receive your donor's stem cells). On Day 0, the day of transplant, you will receive what are known as "stem cells" (cells which will eventually develop into white blood cells, red blood cells and platelets) from your donor. After Day 0, you will be given antibiotics to help fight infections; blood transfusions to increase the number of red blood cells in your system; platelet transfusions to assist in helping your blood to clot; and nutritional and general support.

In an effort to control "graft versus host disease" (or GVHD for short), one of the side effects of transplant discussed further below, your study doctor will recommend **one** of two the following GVHD treatments:

GVHD Option #1 (available only with Transplant Chemotherapy Treatment #1)
You also would receive the drug known as tacrolimus beginning on Day -2 through approximately Day +180 (that is, approximately 6 months after Day 0). Tacrolimus may be given by IV infusion or orally (by mouth). Patients also will receive sirolimus orally starting on Day –2 and continue until Day +180. Finally, another chemotherapy drug, methotrexate, will be given by IV on Day +1, +3, and +6.

GVHD Option #2
You also would receive the drug known as tacrolimus beginning on Day -2 through approximately Day +180 (that is, approximately 6 months after Day 0). Tacrolimus may be given by IV infusion or orally (by mouth). Finally, another chemotherapy drug, methotrexate, will be given by IV on Day +1, +3, +6 and +11.

Depending on your response to treatment, you may require up to three additional infusions of stem cells from your donor. If necessary, your doctor will discuss these treatments with you and they would occur at eight week intervals separating treatments.

Transplant Chemotherapy Treatment #2
Another treatment your doctor might recommend includes the chemotherapy drugs fludarabine, cyclophosphamide, antithymocyte globulin (or ATG for short), and rituximab. The drugs will be

given to you by intravenous (IV) infusion, that is through a needle in a vein in your arm or through a "central line," a catheter (or tube) placed in the large vein under your collarbone or your neck. The day the donor's stem cells will be given to you will be known as Day 0 or the day of transplant. In the description of the treatment that follows, when a drug is given before Day 0, the day of transplant, it will be noted with a negative sign (-). For example, -7 means seven days before Day 0, the day of transplant. When a drug is given after Day 0, the day of transplant, it will be noted with a positive sign (+). For example, +7 means seven days after Day 0, the day of transplant. The first drug to be given will be rituximab. Rituximab will be given by IV infusion on four separate days one week apart. Rituximab will be given on Days -7, -1, +7, and +14 (that is, rituximab will be given seven days *before* Day 0, one day *before* Day 0, seven days *after* Day 0, and fourteen days *after* Day 0) If your donor is not related to you, antithymocyte globulin (or ATG, for short) will be given you to you over six hours on Days -6, -5, and -4 (that is, for three days beginning six days *before* Day 0). Fludarabine will be given by IV infusion over 30 minutes each day for four (4) days on Day -5 through Day -2 (that is, fludarabine will be given five days *before* Day 0). Cyclophosphamide will be given by IV infusion also on Days -5, -4, and -3 (that is, for three days beginning five days *before* Day 0). On Day 0, the day of transplant, you will receive what are known as "stem cells" (cells which will eventually develop into white blood cells, red blood cells and platelets) from your donor. After Day 0, you will be given antibiotics to help fight infections; blood transfusions to increase the number of red blood cells in your system; platelet transfusions to assist in helping your blood to clot; and nutritional and general support.

GVHD Option #2: In an effort to control "graft versus host disease" (or GVHD for short), one of the side effects of transplant discussed further below, you also would receive the drug known as tacrolimus beginning on Day -2 through approximately Day +180 (that is, approximately 6 months after Day 0). Tacrolimus may be given by IV infusion or orally (by mouth). Finally, another chemotherapy drug, methotrexate, will be given by IV on Day +1, +3, +6 and +11.

Depending on your response to treatment, you may require up to three additional infusions of stem cells from your donor. If necessary, your doctor will discuss these treatments with you and they would occur at eight week intervals separating treatments.

Post Transplant Rituximab Maintenance Treatment
All patients, regardless of which transplant chemotherapy treatment is selected by their study doctor, will receive rituximab maintenance therapy every three months for one year beginning three months after Day 0 of transplant. A total of four rituximab maintenance treatments will be given (Month 3, 6, 9, and 12). Blood tests will be obtained every three months during rituximab maintenance therapy.

At any point during your treatment, your doctor may recommend that you take a hormone called G-CSF (granulocyte colony-stimulating factor).

How long will I be in the study?

While undergoing transplant on this study, you will be seen frequently by your study doctor and have laboratory tests. Blood tests will be obtained every three months during the second year, and then every six months for a maximum of 5 years from study entry. CT scans of the chest,

abdomen, and pelvis will be obtained 3 months, 12 months, and 24 months after Day 0 of transplant. While receiving rituximab maintenance therapy, you will be monitored by your study doctor each month prior to rituximab treatments at 3, 6, 9 and 12 months after Day 0. After you complete all treatment on this study, you will then need to be seen by your study doctor and have laboratory tests every six months for a maximum of five years from the date of entry on the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your study doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

The risks and side effects you may experience in this study will be based on the chemotherapy and GVHD treatments your study doctor chooses for you. Below you will find the risks and side effects identified by the treatment (both the transplant **and** the rituximab maintenance treatment) and GVHD treatment.

Risks and side effects related to Transplant Chemotherapy Treatment #1 (Fludarabine, Busulfan, and Rituximab) include:

Likely

- Lowered white blood cell count (neutrophils/granulocytes) that may lead to infection.

- Lowered platelets[v] which may lead to an increase in bruising or bleeding.
- Lowered red blood cells[v] which may cause anemia, tiredness, or shortness of breath.
- Nausea.
- Vomiting.
- Decreased number of a different type of white blood cells (lymphocytes) that may lead to infection.
- Irritation or sores in the lining of the digestive tract (for example, mouth, throat, esophagus, anus, etc.).
- Infusion reactions with rituximab including fever, chills, and nausea which can be severe.
- Loss of appetite and/or weight loss.
- Fatigue.
- Time away from work.
- Hair loss.

[v] Should this occur, it can be treated with blood products (transfusions) and antibiotics.

Less Likely

- Hypertension (high blood pressure) which may require treatment.
- Swelling of the arms or legs.
- High blood sugar level.
- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Your doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection.
- Some other viral infections may be worsened or reactivated from a "sleeping" state in patients with impaired immune function or who receive rituximab.
- Headache.
- Inflammation of the lungs which can cause difficulty breathing and difficulty getting oxygen.
- Infection which occurs due to a decreased number of a type of white blood cells.
- Rejection of your donor's stem cells.
- Graft versus host disease (see below).
- Darkening of the skin.
- Sore throat.
- Abdominal pain.
- Rash or itching.

- Swelling of the lips, eyes, tongue, and throat which can be severe.
- Allergic reaction.
- Stuffy or runny nose, sneezing.
- Allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands.
- Abnormal fast heart beat.
- Decreased blood supply to the heart/heart attack.
- Low blood pressure.
- Excessive sweating.
- Flushing.
- Hives.
- Diarrhea.
- Low blood potassium.
- Dizziness.
- Seizure.
- Pain in the back, joints, or muscles.
- Irritation of the small airways or wheezing.
- Cough.
- Shortness of breath.

Rare But Serious

- Severe reactions during rituximab infusions or severe allergic reaction: a fast heart rate, wheezing, low blood pressure, sweating, swelling of the throat, and face rash may occur within a few minutes of starting treatment. They can be handled with medications and sometimes by slowing the rate of infusion. The reactions are more common during the first infusion of rituximab. You will be given medications to decrease the likelihood that the reactions may occur, and decrease their severity if they should occur.
- Destruction of red blood cells that may be life-threatening.
- Another one of these viral infections causes a serious brain condition called progressive multifocal leukoencephalopathy (PML). PML can be serious causing severe disability or death.
- Vision changes and confusion.
- Abnormal clotting of blood in small blood vessels.
- Rash which may become severe.

- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer.
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of the skin to separate from the middle layer.
- Liver damage that can be severe.
- Infertility/inability to produce children.
- Severe lung dysfunction resulting in the inability to breathe which can be life-threatening.
- Inflammation of the bladder that may cause blood to be present in the urine.
- Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment.

Risks and side effects related to Transplant Chemotherapy Treatment #2 (Fludarabine, Cyclophosphamide, ATG and Rituximab) include:

Likely

- Lowered white blood cell count (neutrophils/granulocytes) that may lead to infection.
- Lowered platelets which may lead to an increase in bruising or bleeding.
- Lowered red blood cells which may cause anemia, tiredness, or shortness of breath.
- Nausea.
- Vomiting.
- Fatigue.
- Irregular menstrual periods in women.
- Hair loss.
- Pain in the abdomen.
- Decreased number of a different type of white blood cells (lymphocytes) that can lead to infection.
- Infusion reactions with rituximab including fever, chills, and nausea which can be severe.
- Irritation or sores in the lining of the digestive tract (for example, mouth, throat, esophagus, anus, etc.).
- Loss of appetite and/or weight loss.
- Time away from work.
- Should this occur, it can be treated with blood products (transfusions) and antibiotics.

Less Likely

- High blood sugar level.
- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Your doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection.
- Some viral infections may be worsened or reactivated from a "sleeping" state in patients with impaired immune function or who receive rituximab.
- Low blood potassium level.
- Headache.
- Swelling of the arms or legs
- Rash, itching.
- Pain in the back, joint, or muscles.
- Lung damage.
- Graft versus host disease (see below).
- Rejection of your donor's stem cells.
- Infection which occurs due to a decreased number of a type of white blood cells.
- Shortness of breath.
- Allergic reaction.
- Stuffy or runny nose, sneezing.
- Allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands.
- Abnormal fast heart beat.
- Abdominal pain.
- Sore throat.
- Decreased blood supply to the heart/heart attack.
- Low blood pressure.
- High blood pressure.
- Excessive sweating.
- Flushing.
- Hives.
- Diarrhea.
- Dizziness.

- Seizure.
- Pain in the back, joints, or muscles.
- Irritation of the small airways or wheezing.
- Cough.
- Inflammation of the lungs which can cause difficulty breathing and difficulty getting oxygen.
- Swelling of the lips, eyes, tongue and throat which can be severe.

Rare But Serious

- Severe reactions during rituximab infusions or severe allergic reaction: a fast heart rate, wheezing, low blood pressure, sweating, swelling of the throat, and face rash may occur within a few minutes of starting treatment. They can be handled with medications and sometimes by slowing the rate of infusion. The reactions are more common during the first infusion of rituximab. You will be given medications to decrease the likelihood that the reactions may occur, and decrease their severity if they should occur.
- Destruction of red blood cells that may be life-threatening.
- Another one of these viral infections causes a serious brain condition called progressive multifocal leukoencephalopathy (PML). PML can be serious causing severe disability or death.
- Abnormal clotting of blood in small blood vessels.
- Liver damage that can be severe.
- Rash which may become severe.
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer.
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of the skin to separate from the middle layer.
- Vision changes and confusion.
- Inflammation of the bladder that may cause blood to be present in the urine.
- Infertility/inability to produce children.
- Severe skin and gut lining reaction that may include rash and sloughing or death of tissue.
- Severe lung dysfunction resulting in the inability to breathe which can be life-threatening.
- Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment.

Risks and side effects related to GVHD Option #1 (Tacrolimus, Sirolimus, Methotrexate) include:

Likely

- Lowered red blood cells[v] which may cause anemia, tiredness, or shortness of breath.
- Lowered white blood cell count[v] that may lead to infection.
- Lowered platelets[v] which may lead to an increase in bruising or bleeding.
- Hypertension (high blood pressure).
- Headache.
- Tremors.
- Difficulty sleeping or falling asleep.
- Condition of the nervous system that causes numbness, tingling, or burning sensation.
- Increased blood potassium level.
- Decreased blood potassium level.
- Decreased blood phosphate level.
- Decreased blood magnesium level.
- Nausea.
- Vomiting.
- Loss of appetite.
- Constipation.
- Diarrhea.
- Abdominal pain.
- Fever.
- Fatigue.
- Increased blood level of an enzyme from muscle.
- Increased blood cholesterol level.
- Weight gain.
- Joint pain.
- Shortness of breath.
- Increased sensitivity to sunlight.

[v] Should this occur, it can be treated with blood products (transfusions) and antibiotics.

Less Likely

- Acne/pimples.

- Rash/itching.
- Hives.
- Infection of the mouth when the white blood cell count is low.
- Infection of the urinary tract when the white blood cell count is low.
- Inflammation or infection of the bladder.
- Chest pain.
- Back pain.
- Upset stomach or heartburn.
- Irritation or sores in the lining of the digestive tract (for example, mouth, throat, esophagus, anus, etc.).
- Dizziness.
- Agitation.
- Anxiety.
- Confusion.
- Convulsion or seizures.
- Depression.
- Hallucinations/delusions.
- Weakness or loss of function caused by damage to nerves.
- Involuntary muscle movement.
- Increased blood level of uric acid, a waste material from food digestion.
- Kidney damage.
- Liver damage.
- Inflammation or infection of the bladder that might result in blood in the urine.
- Fluid collection in the abdomen.
- Swelling of the arms, legs, head or neck, or trunk of the body.
- Increased blood sugar level.
- Blurred vision.
- Ringing in the ears.

Rare But Serious

- Destruction of red blood cells that may be life-threatening.
- Bleeding.

- Severe life-threatening damage to the lungs which can lead to fluid in the lungs.

Risks and side effects related to GVHD Option #2 (Tacrolimus, Methotrexate) include:

Likely

- Lowered red blood cells[v] which may cause anemia, tiredness, or shortness of breath.
- Lowered white blood cell count[v] that may lead to infection.
- Lowered platelets[v] which may lead to an increase in bruising or bleeding.
- Hypertension (high blood pressure).
- Headache.
- Tremors.
- Difficulty sleeping or falling asleep.
- Condition of the nervous system that causes numbness, tingling, or burning sensation.
- Increased blood potassium level.
- Decreased blood potassium level.
- Decreased blood phosphate level.
- Decreased blood magnesium level.
- Nausea.
- Vomiting.
- Loss of appetite.
- Constipation.
- Diarrhea.
- Fever.
- Fatigue.
- Increased sensitivity to sunlight.

[v] Should this occur, it can be treated with blood products (transfusions) and antibiotics.

Less Likely

- Rash/itching.
- Hives.
- Infection of the mouth when the white blood cell count is low.
- Inflammation or infection of the bladder.

- Chest pain.
- Back pain.
- Irritation or sores in the lining of the digestive tract (for example, mouth, throat, esophagus, anus, etc.).
- Dizziness.
- Agitation.
- Anxiety.
- Confusion.
- Convulsion or seizures.
- Depression.
- Hallucinations/delusions.
- Involuntary muscle movement.
- Increased blood level of uric acid, a waste material from food digestion.
- Kidney damage.
- Liver damage.
- Inflammation or infection of the bladder that might result in blood in the urine.
- Swelling of the arms, legs, head or neck, or trunk of the body.
- Increased blood sugar level.
- Blurred vision.
- Ringing in the ears.

Rare But Serious

- Destruction of red blood cells that may be life-threatening.
- Bleeding.
- Severe life-threatening damage to the lungs which can lead to fluid in the lungs.

Risks and Side Effects Related to Post Transplant Rituximab Maintenance Treatment (all patients will receive rituximab maintenance therapy)

Likely

- Decreased number of a different type of white blood cells (lymphocytes) that can lead to infection.
- Infusion reactions with rituximab including fever, chills, and nausea which can be severe.

Less Likely

- Fatigue.

- Allergic reaction.
- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Your doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection.
- Some viral infections may be worsened or reactivated from a "sleeping" state in patients with impaired immune function or who receive rituximab.
- Stuffy or runny nose, sneezing.
- Allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands.
- Lowered white blood cell count (neutrophils/granulocytes) that may lead to infection.
- Lowered platelets which may lead to an increase in bruising or bleeding.
- Lowered red blood cells which may cause anemia, tiredness, or shortness of breath.
- Abnormal fast heart beat.
- Decreased blood supply to the heart/heart attack.
- Low blood pressure.
- High blood pressure.
- Excessive sweating.
- Flushing.
- Hives.
- Rash, itching.
- Diarrhea.
- Vomiting.
- Swelling of the arms or legs.
- High blood sugar level.
- Low blood potassium.
- Dizziness.
- Seizure.
- Pain in the back, joints, muscles.
- Sore throat.
- Abdominal pain.
- Shortness of breath.
- Headache.

- Irritation of the small airways or wheezing.
- Cough.
- Inflammation of the lungs which causes difficulty breathing and difficulty getting oxygen.
- Swelling of the lips, eyes, tongue, and throat which can be severe.
- Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of rituximab given to you.

Rare But Serious

- Severe reactions during rituximab infusion or severe allergic reaction: a fast heart rate, wheezing, low blood pressure, sweating, swelling of the throat, and face rash may occur within a few minutes of starting treatment. They can be handled with medications and sometimes by slowing the rate of infusion. The reactions are more common during the first infusion of rituximab. You will be given medications to decrease the likelihood that the reactions may occur, and decrease their severity if they should occur.
- Rash which may become severe.
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer.
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of the skin to separate from the middle layer.
- Another one of these viral infections causes a serious brain condition called progressive multifocal leukoencephalopathy (PML). PML can be serious causing severe disability or death.
- Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment.
- Severe lung dysfunction resulting in the inability to breathe which can be life-threatening.

Risk of Graft Versus Host Disease (GVHD)

Symptoms of GVHD may include:

- Skin rash
- Liver disease (including jaundice)
- Nausea, vomiting, diarrhea
- Temporary darkening of the skin and hardening and thickening of patches of skin and tissue under the skin (occurs with chronic GVHD)
- Dry and sore mouth and eyes (chronic GVHD)

- Bacterial, fungal, and viral infections (acute and chronic GVHD)
- Weight loss
- Lung disease (chronic GVHD)

Symptoms of GVHD can range from mild to severe, and when severe GVHD can be fatal (may cause death). Medications will be given to prevent or reduce the chances of having severe GVHD, and to treat GVHD if it occurs.

The risk of developing moderate to severe GVHD following transplantation of stem cells from a matched related donor is between 30-50%.

Reproductive risks

The drugs used in this study are known to have risk of causing malformations in an unborn child. Therefore, you should not father a baby while on this study. For this reason, men will be asked to practice an effective method of birth control while participating in this study. Ask about counseling and more information about preventing pregnancy.

Risk of Testing for Infectious Illnesses

Participation in this study will require that you be tested for hepatitis and HIV. Testing for HIV and for the hepatitis viruses may result in a diagnosis of infection with these viruses. In the event that you are diagnosed with hepatitis or HIV, you may be referred to a doctor who specializes in these illnesses. The diagnosis of HIV or hepatitis may result in earlier treatment and/or prevention of many complications from the illnesses. Efforts will be made to keep your personal information confidential. Awareness of a diagnosis of these illnesses may have serious personal and social consequences. Some of these consequences include possible difficulty obtaining health insurance or employment.

Risks and Side Effects Related to Bone Marrow Aspirations and Biopsies

There may be some temporary pain or discomfort associated with these routine procedures, but they are necessary to determine whether you are responding to your therapy. Bone marrow biopsies will be required prior to beginning the study, and 3, 12 and 24 months after Day 0 of transplant.

Secondary Malignancies

A number of established chemotherapy agents have an inherent risk of causing another cancer (secondary malignancy). Certain drugs in use today, not currently known to be associated with this risk, may be shown at a later time to result in the development of these secondary malignancies

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the treatment will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about reduced intensity allogeneic stem cell transplant and rituximab maintenance therapy as treatments for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study, including a bone marrow transplant
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Cancer and Leukemia Group B (CALGB)
- Blood and Marrow Transplant Clinical Trial Network (BMT CTN)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Genentech, the manufacturer of rituximab.

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person: (name)_____ (title)_____ (address)_____ (phone number)_____.

The CALGB has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and

Human Services or for purpose of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Rituximab will be supplied at no charge while you take part in this study. The manufacturer does not cover the cost of getting the rituximab ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the rituximab for some reason. If this would occur, other possible options are:

- You might be able to get the rituximab from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no rituximab available at all, no one will be able to get more and the study would close.

If a problem with getting rituximab occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

Related Research Studies

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

Things to Think About

Many different types of research use normal or diseased (cancerous) specimens. The two main types of research look at

1. Inherited traits that are passed down in families from one generation to the next. For example, researchers may study DNA from blood cells to learn why some cancers are inherited in families, or why a treatment causes side effects in some people but not in others.

2. Changes that happen after you are born (non-inherited). For example, too much soon exposure can cause changes in cells that lead to skin cancer.

Researchers can study DNA (genes), RNA or proteins. When researchers study genes, it is often called "genetic" research, but there is no clear definition for it at this time. Because of this, we use the terms "inherited" and "non-inherited" to explain your choices for donating specimens.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimen is used for this kind of research, the results will not be put in your health records.

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimen that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Cancer and Leukemia Group B may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

We have many ways to protect the information related to your specimens:

1. Your specimens and information receive a unique code. Researchers only receive coded specimens and information, and will not be able to see the key that links the code to you. Only approved people in the Cancer and Leukemia Group B can match you to the code on your specimens and related information.
2. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information.
3. Research studies are reviewed for the quality of the science and for patient protection before specimens are given to researchers. To make sure the research follows the rules of

the Cooperative Group and state or federal laws, records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies.

4. If research results are published, you will not be identified by name or any other personally identifiable information.

About Using Tissue for Research

Specimens for Research (Non-Inherited Research)

During the course of diagnosing your leukemia, your doctor will obtain blood and bone marrow aspirates to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. Additionally, blood (about 2 tablespoonful) will also be obtained at diagnosis and at about seven time points after the transplant (one month, two months, three months, six months, twelve months, twenty-four months after transplant, and if your CLL should ever return). At diagnosis, it may be possible to obtain about 1 tablespoonful of bone marrow aspirate as well. In addition, if you should undergo donor lymphocyte infusions (DLIs, as described above) we would also like to request 2 tablespoonful of blood afterwards. These samples will be obtained when other routine laboratories are obtained so you will not need to undergo additional procedures to collect these samples. We will analyze these samples in the laboratory to see if we can determine how the donor's cells recognize your leukemia cells, and how your immune system recovers after the transplant. Researchers also will examine the particular characteristics of CLL cells and certain molecular and chromosomal features within these cells. The results of these blood studies are for research use only and the results will not be available or used to guide your treatment.

Specimens for Research (Inherited Research)

Researchers would like to investigate whether substances in your blood are related to the way your body responds (or doesn't respond) to the therapy you receive in this trial. Blood taken before treatment (about 1 tablespoonful) will be used to learn how certain genes influence the effectiveness of this therapy in patients diagnosed with CLL. Blood will be taken only once.

This type of research may find medical conditions that affect you and your blood relatives because it looks at inherited traits. While your genes are unique to you, you share some of them with your blood relatives. It is possible that genetic research may find potential health concerns for you or your family. While this situation is rare, information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

We believe that the risks to you and your family from research on inherited traits are very low. Some states have laws that help to protect against genetic discrimination. A federal law (Genetic Information Non-Discrimination Act, GINA) will help reduce the risk from health insurance or employment discrimination once the law goes into effect. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about the GINA law, you can find information about it on the internet or as your study doctor.

While we believe that the risks to you and your family are very low, we cannot tell you exactly what all of the risk are from taking part in DNA research studies. Your privacy and confidentiality will be protected to the fullest extent possible.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. I agree that my specimens may be used for the research studies (specimens for non-inherited research) described above.

Yes *No*

2. I agree that my specimens may be used for the genetic research studies (specimens for inherited research) described above.

Yes *No*

We would like to keep some of the blood and bone marrow specimens that are left over for inherited and non-inherited research for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases.

3. My specimens may be kept for use in research to learn about, prevent, or treat cancer.

Yes *No*

4. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes *No*

5. Someone may contact me in the future to ask me to take part in more research.

Yes *No*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____