

CHRONIC LYMPHOCYTIC LEUKEMIA

Frequently Asked Questions

CLL FAQ
<http://cllfaq@acor.org>

Frequently Asked Questions about Chronic Lymphocytic Leukemia

("CLL FAQ")

Copyright © 1999 - 2005 by David M. Thomas. All rights reserved.

Acknowledgements

Special thanks to Barbara Lackritz, MS (a.k.a. GrannyBarb), Kathy Lebedun, MSW, and Susan J. Leclair, Ph.D., CLS(NCA) for their contributions to this material. Special thanks also to Ben Groot, BSc for his assistance in creating and maintaining the on-line version of this work.

Disclaimer

This document is intended to provide information about chronic lymphocytic leukemia and should not be construed as medical advice. Any information pertaining to your health should be reviewed with your personal healthcare professional.

Copyright

Frequently Asked Questions about Chronic Lymphocytic Leukemia ("CLL FAQ") is the property of David M. Thomas. Permission is granted to download this material without alteration for private and non-commercial use only as long as the following copyright notice is included: Copyright © 1999 - 2005 by David M. Thomas. All Rights Reserved.

Introduction

Frequently Asked Questions about Chronic Lymphocytic Leukemia was originally developed as an on-line resource for the CLL List. Introduced in May 1999, the on-line version of the CLL FAQ is hosted by the Association of Cancer Online Resources, Inc. ("ACOR") a non-profit corporation registered in New York State. The latest version of the CLL FAQ can be found on-line at, <http://cllfaq.acor.org>.

The CLL FAQ is primarily intended for new patients who are dealing with the shock of diagnosis and who are trying to learn about their disease. It is by no means an exhaustive document, but as its name implies, it answers some of the frequently asked questions.

The CLL FAQ was created in North America, which is evident in the language and the terminology that is used throughout. The CLL community, on the other hand, is worldwide, and it is hoped that the language and terminology used in the CLL FAQ will not impact negatively on its usefulness in other parts of the world.

It has been said that it is important to understand and take charge of one's CLL. Hopefully, the CLL FAQ will be a helpful resource in this process.

Contents

General Information

1. What is chronic lymphocytic leukemia (CLL)?.....	1
2. Can CLL be cured?	1
3. Are there other types of leukemia?	1
4. Are there subgroups of CLL?.....	2
5. How common is CLL?	2
6. What causes CLL?	2
7. Is CLL hereditary?	3
8. What are the stages of CLL?	3
9. What is the survival outlook for people with CLL?.....	4
10. What is “smoldering” CLL?	4

Diagnosis, Diagnostic Procedures & Other Tests

11. How is CLL diagnosed?.....	5
12. Should I seek a second opinion?	5
13. What are the blood count basics in CLL?	5
14. What do laboratory reference ranges mean?.....	7
15. What is the difference between percentage of lymphocytes and absolute lymphocyte count (ALC)?	8
16. When do neutrophil counts become a problem?.....	8
17. When do platelet counts become a problem?.....	9
18. What are smudge cells?	9
19. What are immunoglobulins?	9
20. What questions should I ask in early visits with my hematologist?.....	10
21. What is flow cytometry?.....	10
22. What is polymerase chain reaction (PCR)?	12
23. What is the significance of IgV _H gene mutational status in CLL?	12
24. What is the significance of CD38 in CLL?	13
25. What is the significance of bcl-2 in CLL?	14
26. Will I need a bone marrow biopsy and how is it performed?	14
27. What information is detected in a bone marrow biopsy and aspirate?	15
28. What is the significance of beta-2-microglobulin in CLL?	18
29. What is fluorescence in situ hybridization (FISH)?.....	18
30. What does trisomy mean?	18
31. What are some of the main prognostic indicators in CLL?	19
32. What is tissue typing?.....	21
33. What is DiSC assay?	22

Treatment

34. Should I start treatment as soon as possible?	24
35. What are the criteria for starting treatment?.....	24
36. How is CLL treated?	25
37. What drugs are used in treating CLL?	26
38. What questions should I ask prior to chemotherapy?.....	28
39. What side effects should I expect from chemotherapy?	28
40. Where in the CLL treatment plan does transplantation fit?	29

41. Should early stage patients have stem cells harvested for future autologous transplant?	30
42. What is a mini-transplant?	30
43. What is a peripheral blood stem cell transplant (PBSCT)?.....	31
44. What is a cord blood transplant?	31
45. What is leukapheresis?	32
46. What about alternative/complementary therapies?	32
47. Is additional vitamin C recommended for people with CLL?.....	32
48. What is a neutropenic diet?	32
49. What medical centers specialize in treating CLL?.....	33
50. What are clinical trials?.....	33
51. What constitutes a remission in CLL?.....	34
52. What is minimal residual disease (MRD)?	35

Related Disorders

53. Does CLL lead to other forms of cancer?	36
54. What is the difference between CLL and lymphoma?	36
55. What is small lymphocytic lymphoma (SLL)?.....	37
56. What is hairy cell leukemia (HCL)?.....	37
57. What is prolymphocytic leukemia (PLL)?.....	37
58. What is Richter's syndrome?	38
59. What is mantle cell lymphoma (MCL), and is related to CLL?.....	38
60. Is there a connection between shingles and CLL?.....	39
61. What is autoimmune hemolytic anemia (AIHA)?.....	39
62. What is idiopathic thrombocytopenic purpura (ITP)?.....	40
63. What causes night sweats in CLL?.....	41

Other

64. How will CLL affect my normal activities?	42
65. Should people with CLL stop donating blood?.....	42
66. What are some of the dental considerations in CLL?.....	42
67. What are some of the terminal aspects of CLL?	43
68. What should I tell children?.....	43
69. What should I tell colleagues?	44
70. How may I be in touch with other CLL patients?.....	44
71. What are some of the leukaemia-related organizations?	45
Appendix A: Internet Links.....	48
Appendix B: Acronyms	50
Appendix C: Glossary of Terms.....	54

General Information

1. What is chronic lymphocytic leukemia (CLL)?

Chronic lymphocytic leukemia (CLL) is a form of blood cancer in which too many lymphocytes are found in the body. Lymphocytes are a specific type of white blood cell. These abnormal lymphocytes accumulate in the bone marrow, blood, lymph tissue, and other organs of the body. The two main types of lymphocytes are B-cells and T-cells. Approximately 95% of CLL cases involve B-cells; the remainder are T-cell leukemias. The CLL FAQ deals primarily with B-cell CLL.

B-cell CLL is characterized by the relentless accumulation of malignant B-lymphocytes that have an abnormally extended life span and are unable to perform their proper functions. The progressive accumulation of these lymphocytes causes diminished production of normal bone marrow and blood cells.

Some patients have no symptoms at all and are said to be asymptomatic. This “smoldering” condition can continue for many years. Others may experience more rapid onset of symptoms and a more aggressive form of the disease. Symptoms may include enlarged lymph nodes, spleen, and liver. Severe anemia as well as low platelet counts, which can put patients at risk of bleeding, may also occur. Patients with CLL may also develop serious infections because of reduced numbers of infection-fighting cells known as neutrophils.

2. Can CLL be cured?

At this time, CLL remains an incurable disorder; however, treatment can often control the disease and its symptoms.

Many people with CLL continue to have a relatively normal and active lifestyle for many years—in some cases for decades. In this way, CLL is quite unlike acute leukemias, which are far more devastating. Many new treatments for CLL are currently under investigation, and there is good reason for newly diagnosed patients to feel hopeful that long term remissions are reasonably possible. Perhaps a cure is also just around the corner. Bone marrow transplantation currently offers promise as a potential cure, in that several CLL patients who have had bone marrow transplants have had no recurrence of disease.

Patients are encouraged not to panic and not to think of CLL as a “death sentence”.

3. Are there other types of leukemia?

There are several types of leukemia, which differ dramatically in prognosis, treatment, and symptoms. Leukemia is either acute or chronic and usually arises in either of the two main types of white blood cells—lymphoid cells or myeloid cells. When leukemia affects the lymphoid cells, it is called lymphocytic leukemia. When myeloid cells are affected, the disease is called myeloid or myelogenous leukemia. The most common types of leukemia are:

Acute lymphocytic leukemia (ALL) – ALL is the most common type of leukemia in young children. This disease also affects adults, especially those ages 65 and older. ALL can be divided into subcategories by the type of cell or the genetic damage found in the cells.

Acute myeloid leukemia (AML) – AML occurs in both adults and children. This type of leukemia is sometimes called acute nonlymphocytic leukemia (ANLL). AML can be subdivided into categories based on the genetic damage found in the cells.

Chronic lymphocytic leukemia (CLL) – CLL most often affects adults over the age of 55. It sometimes occurs in younger adults, but it almost never affects children.

Chronic myeloid leukemia (CML) – CML occurs mainly in adults. A very small number of children also develop this disease.

These are not the only types of leukemia, but they are the most common forms of the disease.

4. Are there subgroups of CLL?

While CLL has not been formally classified into subgroups, the division of B-CLL into stable and progressive disease was noted in the 1960's, and it is now generally agreed that there are two subsets of CLL based on IgV_H gene mutational status. (see also: What is the significance of IgV_H gene mutational status in CLL?)

As we learn more about CLL and as more sophisticated techniques become available for studying CLL at a molecular level, formal subgroups may be identified. This, in turn, may help to explain why CLL progresses very differently among patients and why response to treatment can vary widely. Some differences in disease progression and response to treatment are no doubt attributable to patient differences such as age and general health, but we may find that additional differences in CLL also exist.

5. How common is CLL?

CLL is the most common form of leukemia in the western world. It accounts for approximately 25 to 30 percent of all leukemias. CLL occurs more frequently in older individuals but is seen increasingly in younger patients as well. It is twice as common in men as in women. Approximately 1.8 to 3 new cases per 100,000 Americans are diagnosed each year. In the age group 35 to 59, the annual incidence rises to 5.2 new cases per 100,000 Americans, and in the age group 80 to 84, it rises further to 30.4 new cases per 100,000 Americans.

6. What causes CLL?

The cause or causes of CLL are not known. Scientists know that CLL occurs in males more often than females and in white people more often than in black people. However, they cannot explain why one person gets CLL and another does not.

7. Is CLL hereditary?

Clusters of CLL in families have been reported, and first-degree relatives of patients with CLL have a threefold-increased risk for CLL compared with the general population.

8. What are the stages of CLL?

Staging for CLL is used primarily for treatment planning. Two frequently used staging systems are the Rai system and the Binet system. The Rai staging system was introduced in the mid 1970's, and a modified version was introduced in 1987. Both the original Rai staging system and the modified version are still in use. The Rai staging system is used primarily in North America while the Binet staging system is commonly used in other parts of the world.

In any stage, treatment planning is different for disease that has not responded to treatment (refractory disease) than for newly diagnosed and untreated disease. Details of the Rai and Binet staging systems are:

Rai Staging System

Stage 0 – There are too many lymphocytes in the blood, but there are usually no other symptoms of leukemia. Lymph nodes and the spleen and liver are not swollen, and the number of red blood cells and platelets is normal.

Stage I – There are too many lymphocytes in the blood and lymph nodes are swollen (lymphadenopathy). The spleen and liver are not swollen and the number of red blood cells and platelets is normal.

Stage II – There are too many lymphocytes in the blood, lymph nodes are swollen, and either the liver is swollen (hepatomegaly) or the spleen is swollen (splenomegaly).

Stage III – There are too many lymphocytes in the blood and too few red blood cells (anemia). Lymph nodes and the liver or spleen may be swollen.

Stage IV – There are too many lymphocytes in the blood and too few platelets (thrombocytopenia). The lymph nodes, liver, or spleen may be swollen, and there may be too few red blood cells (anemia).

Modified Rai Staging System

Low-risk group – Rai Stage 0 (lymphocytosis only – blood and marrow).

Intermediate-risk group – Rai Stage I (lymphocytosis and enlarged nodes) and Stage II (enlarged spleen and/or liver) combined.

High-risk group – Rai Stage III (lymphocytosis with anemia, defined as hemoglobin of less than 11 gm%) and Stage IV (platelets of less than 100,000 per microliter of blood) combined.

Binet Staging System

Clinical stage A – Red blood cells and platelets are in the normal range and there are fewer than three areas of lymphoid involvement.

Clinical stage B – Red blood cells and platelets are in the normal range and there are three or more areas of lymphoid involvement.

Clinical stage C – Below normal numbers of red blood cells (anemia) and/or platelets (thrombocytopenia) regardless of the number of areas of lymphoid involvement.

Some consideration has been given to an integrated system utilizing both the Rai and Binet staging systems. According to the integrated system, each Binet stage is further identified by the appropriate Rai stage (e.g., A-0, A-I, A-II, B-I, B-II, C-III, C-IV). The integrated system has not been widely accepted, and most physicians continue to use either the Rai or Binet system. The Rai and Binet systems are not the only staging systems for CLL, but they are the most widely used systems.

9. What is the survival outlook for people with CLL?

The National Cancer Institute-Sponsored Working Group (NCI-WG) recommends usage of the “3-risk group” modification of the original five-stage Rai staging system. The “3-risk group” modification is as follows:

- Low-risk group – Rai Stage 0 (lymphocytosis only – blood and marrow).
- Intermediate-risk group – Rai Stage I (lymphocytosis and enlarged nodes) and Stage II (enlarged spleen and/or liver) combined.
- High-risk group – Rai Stage III (lymphocytosis with anemia, defined as hemoglobin of less than 11 gm%) and Stage IV (platelets of less than 100,000 per microliter of blood) combined.

The median life expectancy of patients in the low-risk group is 14+ years, the intermediate-risk group 8 years, and the high-risk group about 4 years. For additional perspective on medians, there is an excellent article entitled, The Median Isn't the Message, which is available at http://www.cancerguide.org/median_not_msg.html.

10. What is “smoldering” CLL?

In early-stage disease (Rai Stage 0 to II), a group of patients with “smoldering” CLL has been identified. These patients have hemoglobin of more than 13 grams per deciliter of blood (13g/dL), platelet count of greater than 150,000 per microliter, and lymphocyte count of less than 30,000 per microliter. They also have a doubling time of peripheral lymphocytes of longer than 1 year and non-diffuse bone marrow histology. These patients have a survival equivalent to an age- and sex-matched population.

Diagnosis, Diagnostic Procedures & Other Tests

11. How is CLL diagnosed?

CLL is often discovered by chance when people have routine blood tests. Most of these people will have no symptoms at the time of diagnosis. CLL is suspected when blood tests reveal excessive numbers of lymphocytes. Excessive is defined by a number which can be reported in a variety of ways. There needs to be an absolute increase of lymphocytes, which is frequently seen in the complete blood count (CBC) report as either LY# or LY-ABS. Lymphocytes are said to be absolutely increased when the number is above 5.0×10^9 raised to the 9th power per liter of blood or 5.0×10^3 raised to the 3rd power in a microliter of blood. An older system would write this as 5,000 cells per microliter of blood, and many physicians still use this as it is easier to say. Most patients typically have more than two to three times this number of malignant lymphocytes at the time of their diagnosis.

Diagnosis is often confirmed via a bone marrow biopsy (BMB) or via a blood test called flow cytometry. Other symptoms that may be present at diagnosis include fatigue, lack of energy, a general feeling of ill health, loss of appetite, enlarged lymph nodes, enlarged spleen, low-grade fever, weight loss, anemia, frequent infections, bruising/bleeding, bone or joint pain, and night sweats.

12. Should I seek a second opinion?

It never hurts to seek a second opinion. Most CLL patients will be initially diagnosed and cared for by community hematologists/oncologists whose experience with CLL will likely be limited. Very few CLL patients will be fortunate enough to have immediate access to a CLL specialist.

For those who don't have access to CLL specialists in their communities, it may be worthwhile to travel to see a specialist. Many specialists will work with local physicians in the treatment and management of CLL. A directory of CLL specialists published by the CLL Foundation can be found on line at, <http://www.clfoundation.org/DrDirectory.aspx>.

Perhaps the most important times to seek a second opinion are at the critical junctures in CLL: initial diagnosis, the point of requiring treatment, and when treatment fails and the patient must look at other options.

13. What are the blood count basics in CLL?

Understanding changes in basic blood counts is important in monitoring and managing CLL. There are three major types of blood cells: red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes).

Red blood cells (RBC's) are the major component of blood. They carry oxygen and carbon dioxide throughout the body. The percentage of red blood cells in the blood is called the hematocrit. The part of the red blood cells that carries oxygen in a protein is called hemoglobin.

One calculation that is very important is the absolute cell count. This is achieved by multiplying the total white cell count by the percent of a specific cell reported. Based on these figures, the normal lymphocyte count is in the range of 1,000 to 3,850 per microliter of blood or $1.0 - 3.8 \times 10^9/L$. Often the first symptom of CLL is an above normal lymphocyte count, which is discovered in a routine blood test.

14. What do laboratory references ranges mean?

Reference range values are for apparently healthy individuals. Every laboratory should have developed its own reference ranges for all of the procedures it performs. While all laboratories' ranges will be close, there will be variations due to collection, storage, transport, preparation techniques, types of instruments used, and the specific patients in the laboratory's population.

Reference ranges are calculated by performing the same test on a number of "assumed healthy" people that mirror the age or gender of the population that is of interest. The greater the number of individuals in the pool, the more valuable the range will be. Once the results are finalized, an average (mean) is calculated. The next step is similar to a teacher putting a class's grades onto a Normal (Gaussian) Curve. The calculation is called a standard deviation. The range of ± 2 standard deviations should be wide enough that 95% of all of the test results should be included. This is the reference range.

Since the ranges that are developed are averages, not a definition of "normal", the best way to look at these values is as a reference—something with which to compare yourself against others in your situation. The best comparison, however, is against your own previous reports.

In the US, the reference range for total white blood cell counts is 4,000 to 11,000 or $4. - 11. \times 10$ raised to the 9th power per liter or $4. - 11. \times 10$ raised to the 3rd power per microliter. The various types of white blood cells are often expressed as a percentage of the total white blood cell count. Usual percentage ranges are as follows:

- Basophils – 0 to 2%
- Eosinophils – 0% to 3%
- Lymphocytes – 25% to 35%
- Monocytes – 3% to 10%
- Neutrophils – 50% to 60%

These percentages are derived from 1) a microscopic examination of blood performed manually in which some hundreds of cells are differentiated from each other (this procedure is called a differential or diff) or 2) a machine scored differentiation based on cell patterns.

Absolute counts are calculated by multiplying the total white blood cell count by the percent of the specific cell line in which you are interested. A percentage of 50% neutrophils in a total white blood cell count of 6,000 equals an absolute neutrophil count of 3,000. While percentage reports are considered adequate for most patients, absolute values are more important for patients with hematologic disorders.

In order to minimize variations based on laboratory differences, CLL patients who are tracking their counts may want to always use the same lab for their blood count evaluations. It's important to remember that these statistics work only on populations, not on individuals. You need to compare yourself to you, not a scale.

15. What is the difference between percentage of lymphocytes and absolute lymphocyte count (ALC)?

Absolute counts are extremely important. If lymphocyte or other counts are reported as percentages of the total white blood count (wbc), the absolute values can be calculated as follows: Total wbc x % cell type reported ÷ 100. This formula can be used for calculating the absolute lymphocyte count, absolute neutrophil count, etc.

By way of example, if the total white count reported is 25,000 and the percentage of lymphocytes reported is 80%, the calculation is as follows: 25,000 x 80 ÷ 100. The result is an absolute lymphocyte count of 20,000.

If the total white blood count minus the total lymphocytes is less than 2000, the patient becomes increasingly at risk of infection. This is one of the reasons it is essential to monitor absolute counts, not percentages.

16. When do neutrophil counts become a problem?

As CLL progresses excess lymphocytes in the bone marrow compromise the production of other blood cells. Chemotherapy aimed at reducing lymphocytes also reduces other blood cell counts.

One of the cell types that is important for CLL patients to monitor is neutrophils. Neutrophils are a type of white blood cell and are an important defense against infection, especially bacterial infection. Neutrophils are also referred to as granulocytes, polys, bands, PMNs, segs, and nonsegs. When neutrophil counts become too low (neutropenia), patients are at risk of infection.

Normal neutrophil counts are between 2,000 and 8,000 (2.0 to 8.0) per microliter of blood. Many laboratories will also report this as 2.0 - 8.0 x 10.0⁹/L. The numbers 2.0 - 8.0 remain the same but have been adjusted to reflect the larger volume of blood. Experience has shown that neutrophil counts above 2.0 will keep almost everyone safe from infections. Patients with counts between 2.0 and 1.0 should take precautions such as staying away from crowds, children with runny noses, etc. Between 1.0 and .5, patients are in jeopardy of infections from everyday bacteria found in salads, fresh unpeeled fruit, shellfish, rarely cooked foods, etc. Below .5 most physicians consider that patients already have infections, usually from their own bacteria, in the gastrointestinal tract, nose, etc. (see also: What is a neutropenic diet?)

When neutrophil counts fall too low because of advancing disease and/or chemotherapy, physicians may administer granulocyte colony-stimulating factors (G-CSF) to boost neutrophil counts. G-CSF is also known as filgrastim or by its trade name Neupogen™.

If neutrophil counts are reported as percentages, patients can calculate absolute neutrophil counts (ANC) by multiplying the total white blood count by the percentage of neutrophils. While percentage reports are considered adequate for most patients, absolute values are more important for patients with blood (hematologic) disorders.

17. When do platelet counts become a problem?

Platelets prevent excessive bleeding by helping blood to clot at the site of an injury. An abnormally low platelet count (thrombocytopenia) may result in small vessel bleeding that can cause small red dots on the body (petechiae), or in excessive bleeding from wounds in mucous membranes, skin, or other tissues (ecchymoses and hematomas).

Platelet counts in CLL patients can become compromised by excessive lymphocytes, by treatment, and by related conditions such as Immune Thrombocytopenic Purpura (ITP).

Normal platelet counts are between 150,000 and 350,000 ($150 - 350 \times 10^3 \mu\text{L}$ or $150 - 350 \times 10^9\text{L}$) per microliter of blood. There are no clear-cut numbers for when platelet counts become a concern. As oncologists gain more experience with decreased platelet counts, the threshold of concern has dropped. It used to be that anyone with a platelet count of lower than 75 was a candidate for platelet transfusion; now it is down into the 10's and 20's - lower yet if there is no sign of bleeding.

Platelet counts below 20 are of serious concern, but anyone is at risk of bleeding episodes if the platelets are decreased below 75.

18. What are smudge cells?

Patients often see a reference to smudge cells in their complete blood count (CBC) reports. Smudge cells are cells that are probably damaged during the CBC process. The cell walls rupture, and when seen under the microscope, they look like a smudge; hence the term smudge cells. These cells are probably lymphocytes and are so distorted that they can't be given a "real" name.

Smudge cells are not unique to CLL. However, they are seen much more frequently and in much higher numbers in CLL than in any other condition. For example, in normal specimens, there may be .01 percent. In patients with severe infections or burns, there may be 0.1 to 0.3 percent. In patients with acute leukemias, there may be as many as 1 to 3 percent, but in CLL patients, smudge cells can be up to 20 percent of all cells, or higher.

19. What are immunoglobulins?

Immunoglobulins are proteins called globulins, specifically immunoglobulins (Ig) or antibodies (Abs). They are made by B-lymphocytes and appear on the outside of cells when seen under the microscope. The antibodies that these cells produce are in response to the presence of foreign substances called antigens.

B-lymphocytes make five different types of antibodies: IgA, IgG, IgM, IgE, and IgD. The type of antibody produced is based on the type of antigen detected and the method of stimulation. IgE, for example, is the response of choice for allergic reactions.

For the most common antigens, (flu, viruses, and the like) the first antibody made is usually IgM. How the antigen got into the patient's system also plays a role. IgA is usually made if the antigen was found in body fluids such as saliva while IgM usually

responds to GI tract antigens. IgG is the first responder for blood borne items and the final choice for more antibodies.

Eventually, the antibody destroys the antigen, and a small number of cells settle into a memory state. They are no longer making the antibody, but the next time they recognize that specific antigen, they will react faster and more efficiently. This "memory" cell is the cell responsible for the protection we have from vaccinations.

Normal levels of immunoglobulins vary somewhat, but are typically as follows:

- IgG: 5.5 – 19.0 g/L (grams per liter of blood)
- IgA: 0.60 – 3.3 g/L (grams per liter of blood)
- IgM: 0.45 - 1.5 g/L (grams per liter of blood)
- IgD: 5 - 30 mg/L (milligrams per liter of blood)
- IgE: <500 ug/L (micrograms per liter of blood)

When responding to antigens, these levels will rise.

CLL patients—particularly those with progressive disease—may not be capable of producing sufficient quantities of immunoglobulins in which case their ability to fight infections may be diminished. In these cases, patients are sometimes given immunoglobulins intravenously to help them fight infections.

20. What questions should I ask in early visits with my hematologist?

Following are some of the questions to ask in early visits to your hematologist:

- What do the blood tests show? How is this different from “normal”?
- What stage am I in?
- Will I need further tests? How often will they be?
- Will you mail or fax copies of my test results, or should I come in to pick them up? If I pick them up, when will they be ready?
- What symptoms should I watch for?
- What changes should I make to my daily routine to avoid complications?
- When do I see you and when do I see my family Doctor?
- When do you anticipate that I will require treatment?
- How many CLL patients do you have?
- How do you anticipate treating my CLL?
- What is the long-term outlook for my CLL?

21. What is flow cytometry?

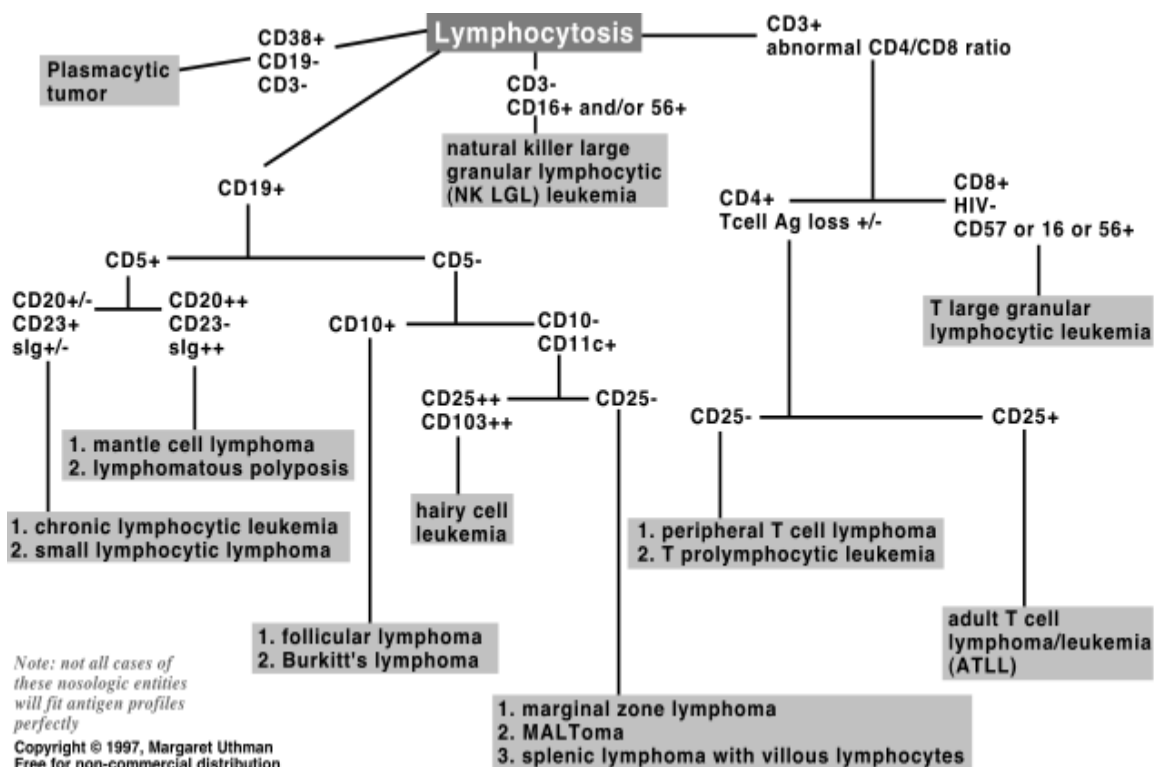
Flow cytometry is a diagnostic technique that is used to measure the chemical or physical characteristics of cells in suspension. Flow cytometry can also determine the types and the quantities of antigens expressed on cell membranes through a process called immunophenotyping. Antigens are substances that are capable of activating the immune system. Each antigen category is called a cluster of differentiation (CD) and is numbered.

This is very much an evolving field. Isolation of CD markers is continuing and new ones are being found monthly. As a result, marker panels will change, and more specific information will be available. As a general rule, it can be said that,

- Cells that are positive for CD2, 3, 4, 5, 8, 45RA and/or 45RO are T-lymphocytes.
- Cells that are positive for CD10, 19, 20, 21, 23, 35, 40, and sometimes 77 are B-lymphocytes (CD5 can also be found on a specific subset of B-lymphocytes).
- CD28 can be positive with T or B-cells and NK (natural killer) cells, which are another lymphocyte subset.
- CD34 is one of the most important markers for it is seen in the hematopoietic pluripotential stem cell (PSC) which is the cell that is "wanted" in bone marrow or peripheral blood stem cell transplants.
- CD38 is a receptor that is found in plasma cells, some thymocytes (early lymphocytes still in the thymus), NK cells, and in very early B-cells. Increased presence of CD38 has been found in cells in multiple myeloma, and certain acute lymphoblastic and myeloblastic leukemias. CD38 is also thought to be of predictive value in determining the clinical course that CLL will take.

In CLL cells, a distinct pattern of antigens is expressed. CLL lymphocytes coexpress the B-cell antigens CD19 and CD20 along with the T-cell antigen CD5. The analysis of a blood sample by flow cytometry is therefore very useful in confirming the diagnosis of CLL.

The following diagram illustrates how CD markers are used in the diagnosis of disorders that are characterized by elevated lymphocyte counts (lymphocytosis). It is presented here with permission of the copyright holder, Dr. Margaret Uthman.



The terms kappa and lambda, which appear on flow cytometry reports, refer to portions of the immunoglobulin or antibody molecule. Kappa and lambda are long chains of amino acids. While there are heavy chains and light chains, kappa and lambda are both light chains. Most people should be able to make either of these light chains in the amounts appropriate for antibody activity. Over expression of one of the chains is often seen in CLL patients and usually means a loss of control by the cells.

When the leukemias were first discovered, the only tool available was the microscope. Now we have learned how to identify cells by their cell membranes. It is hoped that we will soon be able to identify cells by their DNA.

Flow cytometry is very time consuming to perform. Cells cannot be tested for every known antigen—it's too expensive, requires too much time, and there is too great a possibility of error. For these reasons, every lab makes a series of decisions concerning which tests will be run on which samples.

In CLL, malignant lymphocytes derive from cells gone berserk (monoclonal expansion). If we can find out what type of cell it is (for example, does it have a compound on its membrane called CD20), then it is possible to design a drug (monoclonal antibody) to fight only CD20+ cells. This is the underlying principle of medications like rituximab (Rituxan).

22. What is polymerase chain reaction (PCR)?

Polymerase Chain Reaction, (PCR) is a laboratory process that was developed in 1985. In PCR, a particular DNA segment from a mixture of DNA chains is rapidly replicated, (between 10,000 and 1,000,000 copies can be made, depending on the procedure) producing a large, readily analyzed sample of a piece of DNA. The process is sometimes called DNA amplification. PCR has had an immense impact on biology and medicine, especially genetic research.

PCR is commonly used in CLL to test for minimal residual disease (MRD) in patients who have achieved complete remissions. This technique is very sensitive and is capable of detecting a single CLL cell in 100,000 cells.

PCR can be performed on any number of specimens: tissue, bone marrow, peripheral blood, and fluids. It is usually performed on the specimen that is thought to harbor the cell line of interest. In CLL, PCR is typically performed using the bone marrow or the peripheral blood (a normal blood draw). Because the leukemias arise in the marrow, some physicians prefer to perform PCR using a marrow specimen.

The presence of minimal residual disease in patients who have achieved complete remissions is predictive of a shorter event-free remission. For this reason, when minimal residual disease is detected, further treatment aimed at eradicating residual CLL cells may be recommended.

23. What is the significance of IgV_H gene mutational status in CLL?

The division of B-CLL into stable and progressive disease was noted in the 1960's, and today, it is generally agreed that there are two subsets of CLL based on IgV_H gene mutational status. Patients with unmutated immunoglobulin V genes (approximately

40%) form one subset while patients with mutated immunoglobulin V genes form the other subset. There is no evidence that the subsets change from one into the other. The unmutated subset is three times as common in men while the mutated subset is equally common in men and women.

These two subsets of CLL have separate and distinct natural histories. Early stage patients with unmutated immunoglobulin V genes have a median life expectancy of 8 years, while those with mutated immunoglobulin V genes have a median survival of twenty-five years. It is not correct to assume that all CLL patients with mutated immunoglobulin V genes are smoldering, since some cases do progress to advanced stage disease. However, it is very likely that all cases of smoldering CLL are confined to patients with mutated immunoglobulin V genes.

The best specimens for testing IgV_H gene mutational status are the peripheral blood and the bone marrow. To be absolutely certain, both should be evaluated since there are patients who express this mutation in the marrow, but not in the peripheral blood. The best test for IgV mutational status involves sequencing of IgV_H genes. Another option is single-cell reverse transcription-polymerase chain reaction (RT-PCR). Both of these procedures are expensive and are not readily available. For this reason, researchers look for surrogate markers that are strong predictors of IgV_H mutational status.

Some researchers believe CD38 is an accurate surrogate for IgV_H mutational status—patients with less than 20 percent CD38+ B-CLL cells are likely to have mutated immunoglobulin V genes while patients with greater than 20 percent CD38+ B-CLL cells are likely to have unmutated immunoglobulin genes. This is a matter of ongoing debate as it appears that there is approximately a 30% discordance between the assays. Moreover, in 25% of cases the expression of CD38 changes during the course of the disease. Serum thymidine kinase level is thought to be another surrogate marker where >15 U/l has proved to be a strong predictor of mutational status.

24. What is the significance of CD38 in CLL?

The presence of the antigen CD38 on B-CLL cells is a much discussed prognostic indicator in CLL. Whether it is a truly independent prognostic indicator or simply a reflection of IgV_H gene mutational status, CD38 clearly seems to have some relevance in predicting whether a patient's CLL is likely to have a favorable or unfavorable clinical course. CD38 is detected by flow cytometry, a diagnostic technique frequently used in confirming CLL.

Patients with less than 20 percent CD38+ B-CLL cells are likely to have a favorable clinical course requiring minimal or no therapy. Patients with equal to or greater than 20 percent CD38+ B-CLL cells are more likely to have an unfavorable clinical course requiring earlier and ongoing treatment. Significant differences in survival are also thought to exist between these two groups. CD38 expression remains stable over time in the majority of patients, but it is known to change in approximately 25 percent of cases. Its level of expression does not seem to be influenced by chemotherapy.

The connection between CD38 expression and IgV_H gene mutational status is not well understood. It appears that patients with less than 20 percent CD38+ B-CLL cells are likely to have mutated IgV_H genes while patients with greater than 20 percent+ B-CLL cells are more likely to have unmutated IgV_H genes. While this is often the case, there is

approximately a 30 percent discordance between assays for CD38 and IgV_H mutational status (see also: What is the significance of IgV_H gene mutational status in CLL?)

Both CD38 and IgV_H gene mutation are thought to be useful prognostic indicators in B-CLL, but because of the relative ease of testing for CD38, it is a much more convenient test.

CD38 and IgV_H mutational status are just two of a number of prognostic indicators in CLL. Others include, circulating levels of beta-2-microglobulin and soluble CD23, lymphocyte doubling time, serum thymidine kinase levels, bone marrow histology, and chromosome abnormalities.

25. What is the significance of bcl-2 in CLL?

Bcl-2 is one of several proteins that positively and negatively regulate cell death. Bcl-2 inhibits programmed cell death and is consistently over-expressed in B-CLL patients. This over-expression of bcl-2 that occurs in many forms of leukemia contributes to the relentless accumulation of lymphocytes that fail to die and to their resistance to chemotherapy.

In the laboratory, Antisense drugs such as Genasense™ have demonstrated an ability to inhibit bcl-2 expression in CLL, thereby reducing resistance to programmed cell death and to chemotherapy. Antisense treatment is currently being tested in clinical trials, followed by state-of-the art anticancer therapy in an effort to improve patient outcome.

26. Will I need a bone marrow biopsy and how is it performed?

Yes, in all likelihood, you will be asked to undergo a bone marrow biopsy at some point in your diagnosis or treatment. In some major cancer centers, bone marrow biopsies are not performed until treatment begins.

There are two procedures used for obtaining bone marrow samples: the bone marrow aspirate which is used to obtain a small amount of marrow from inside the bone, and the bone marrow biopsy which is used to obtain a sample from the bone showing the structure of the bone marrow cavity.

Aspiration works extremely well when there is little or no fibrosis (when the cells in the marrow are not tightly packed) and when some cells are individual (not so tightly bound to each other that they look like a single entity). This is because of the need to force single cells to come into the syringe by applying a vacuum. Biopsies work well when there are decreased numbers of cells or the cells form tight packets. Many facilities perform both in the same procedure. The aspirate is done first and then the “core” biopsy is performed. This provides the best of both worlds with only one needle insertion.

These procedures are useful in confirming CLL, determining the extent of the disease, and deciding on treatment. The pattern of lymphoid infiltration in the biopsy specimen of the marrow also provides useful prognostic information—diffuse involvement correlates with progressive or advanced disease, while nodular or interstitial (non-diffuse) patterns predict a better prognosis.

The samples are usually obtained from the back of the hip bone, although the breast bone (sternum) may be used instead for bone marrow aspirates only. These procedures cause some brief and usually mild discomfort. They are usually carried out with local anaesthetic, although oral or intravenous sedation may also be available.

27. What information is detected in a bone marrow biopsy and aspirate?

Before the invention of immunophenotyping, examination of the bone marrow was the required method of diagnosing CLL. By agreed definition, anyone whose lymphocytes made up more than 30% of the blood cells in the marrow was presumed to have CLL. That, together with the signs, symptoms, and a complete blood count (CBC) of the peripheral blood made the diagnosis.

Bone marrow biopsies are no longer required to diagnose CLL, but biopsies and aspirates are regularly used to assess disease extent, degree of marrow involvement, effect of treatment, and readiness for transplant.

Bone marrow biopsies and aspirates look very much alike. They are drawn from the same sites; they even use the same insertion needle. They are different in the type of specimen that they withdraw. Biopsies take a solid core of marrow with all of its structures such as capillaries and collagen fibers intact. Aspirates sacrifice the architecture of the marrow in order to spread the cells out more thinly so that the individual cells can be evaluated. Some conditions can be evaluated just by biopsy; others just by aspirate. Many physicians prefer to obtain both types of specimens so that a more complete picture of the marrow can be seen. It is a difficult specimen collection, so it makes sense to get as much information as possible with a single needle.

The bone can be thought of as a commercial honeybee hive. The object is to get through the outer structure of the hive without damaging it and take some of the honeycomb and some of the honey. The marrow, which is represented as the honeycomb, is three-dimensional and contains significant numbers of support structures such as collagen, arteries, veins, capillaries, and lymphatics. The aspirate, which is the honey, contains the developing blood (hematopoietic) cells.

Bone Marrow Biopsy

In bone marrow biopsies, an extremely sharp but hollow needle-like tool is placed into the marrow and twisted. The piece of marrow inside the hollow is removed as a unit with all of its cells and structures untouched. This is the biopsy material and it is treated in the histology laboratory the same way that one treats biopsies of lymph nodes, of breast tissue, or any other tissue.

This specimen is placed into hot wax (paraffin), which permeates the entire specimen giving it strength and rigidity. It is then cut into extremely thin sections (approximately 4-6 millionths of an inch). These sections are then stained and the physician examines them under the microscope. It is then possible to see if there is any damage to the structure of the marrow. Are there, for example, increased amounts of scarring (fibrosis)? Is there damage to the vessels (arteries, veins, and capillaries) that provide the marrow with nutrients? Is there sufficient iron storage in the tissue cells? It is in this sample that one can evaluate cellularity. As one ages, the number of hematopoietic cells lessens, and the amount of fat increases. Cellularity can only be evaluated if you know for sure that you have a sample that contains all of the cells in a given volume, so cellularity is only

reported on a biopsy or clot section. Overall numbers of cell types can be identified and how they are grouped together can be viewed as well.

Bone Marrow Aspirate

One of the drawbacks to a biopsy is that many of the cells cannot be seen well. This is primarily because the stain used is not specific to hematopoietic cells, but also there is the issue of the damage that is done to the cells in the treatment process. While individual cells are seen, the processing concentrates on structure and relationship, not on individual cells. To see individual cells requires a clear separation of cells. In order to accomplish this, a drop or two of liquid marrow is placed on a slide, and another slide is placed on top of it, and the specimen is squeezed between the two slides, causing it to spread out. This spreading destroys any structural components, but it provides a thin, well-separated coating of marrow across the slide. When this is stained with the usual stains found in a hematology laboratory, one can view the smear with a microscope and identify individual cells and assess their quality.

It is from the aspirate that a differential report is produced showing percentages of different cell lines. The differential section of biopsy/aspirate lab report looks similar to a complete blood count (CBC) report, but it is performed by identifying between 500 and 1000 cells instead of the traditional 100 cells used in the peripheral blood differential. The percentage of lymphocytes shown in this section of the report represents the percentage of marrow involvement that is often quoted in CLL. This percentage is a key indicator in determining the extent of disease, the efficacy of treatment, and in preparing patients for transplant. Most transplant centers want this percentage to be below ten percent prior to transplant.

Common Processes

Multiple slides of each type of specimen are evaluated and each type of material will have its place in the report. As a consequence, it may appear that the report contains the same thing over and over. It does. It is possible for a report to contain 2 different slide reports from the biopsy, 2 reports from the aspirate and reports from additional or special staining techniques. Why multiple slides? Many conditions are very focal, and appear in small discrete places. If only one slide was evaluated, the condition might be missed entirely. In some institutions, marrows may be checked by a minimum of 4 slides from each type of specimen.

Each slide is evaluated and the total impression is reported. The steps listed are performed on each slide. Different steps are performed with differing levels of magnification. For some steps, a small amount of magnification is needed; for others a very high amount of magnification is needed.

At the lowest level of magnification, the first step is to confirm that there are spicules of real bone marrow present. It is possible to get just fat deposits or just blood. Without the spicules, you cannot tell if what you are looking at is really a reflection of the marrow or just material that was picked up by the aspiration. So you will see on the report some comment about the quality of the aspirate that mentions spicules. If you or your physician sees that the specimen was poor or good, then you can interpret the results in the light of that comment.

The next step in the evaluation assesses the relative cellularity of the specimen. This is best done on the biopsied material and not the aspirate but many times there will be a confirmatory comment about cellularity on an aspirate's report. In general, as one ages, the cellularity of the marrow declines and that space is used by fat cells. Newborns have essentially no fat and 100% cellularity while an eighty year old will have approximately 60% fat and 40% blood producing cells. If the marrow is under stress and can increase the number of blood producing cells, then the cellularity will be increased. The next step is to scan the slide for the presence of any large abnormal cells or clumps of cells. Malignant cells tend to adhere to each other so they may be in abundance in one portion of the slide and not in another. The cells from which platelets arise (megakaryocytes) are also evaluated. These cells are quite large and relatively few in number so you scan the entire slide to get a sense of how many are present. It is important for megakaryocytes to be present in adequate numbers and to be seen to be producing platelets.

At the next magnification level, the Myeloid to Erythroid (M:E) ratio is performed. Since red cells live significantly longer than white blood cells, usually there are three to four times the number of white cell precursors to red cell precursors. On the slides containing biopsied material, comments about the support structure, the vessels, bone cells, and collagen are made.

At the highest level of magnification, individual cells are evaluated and comments are made about their numbers and quality. At this point comments about the exact appearance of the abnormal lymphocytes are made. In CLL, commonly used words are "monotonous in appearance" or "clonal expansion". The red cell precursors are evaluated to see if there are problems with hemoglobin synthesis (most typically from iron deficiency) or if there are problems with the nucleus (most typically from folic acid deficiency) or if they are adequate in number. These comments support the CBC's hemoglobin, hematocrit, and red cell indices results. Finally, the platelet production is evaluated. By looking at megakaryocytes, one can see if they are producing platelets and if the platelets being produced are appropriate looking.

Special testing

One test that is routinely performed on bone marrow biopsy material is a test for iron deposits. This requires the use of a different stain so while it is a routine test it is usually thought of as a special stain. In this stain, iron deposits are stained blue while the cells themselves stain pink. The absence of any blue deposits confirms that the person lacks adequate iron and is either iron deficient or barely able to keep up with need. In addition to certain inherited conditions, there are a number of ways in which a person may have too much iron stored. One of the more common ways is by repeated transfusions. Another is by using too little iron because there is a suppression of red cell production since hemoglobin production accounts for over 90% of all iron in the body. Iron stores will not tell which process is involved but will provide the physician with a needed piece of information for treatment decisions.

Additionally, marrow cells can be tested by flow cytometry, cytogenetics, FISH, or PCR techniques. This is important because there are situations in which malignant cells will be found in the marrow only or in the nodes only or in the peripheral blood only. Close

monitoring of where the malignant cells are is important in prognosis as well as treatment.

28. What is the significance of beta-2-microglobulin in CLL?

Beta-2-microglobulin (β 2M) is a protein found on the surface of all cells. Small amounts are shed into the serum and are usually filtered out by the kidneys. Increased amounts are found in the serum of patients with kidney disease, lymphomas, some leukemias, and myelomas.

Of interest is the prognostic connection that is sometimes seen with this protein, especially with myeloma, but in the other conditions as well. People diagnosed with these diseases and who have levels of beta-2-microglobulin below 2.0 (2mg/L) seem to have at least 2 more relatively complication-free years. Beta-2-microglobulin is evaluated via a normal blood draw.

29. What is fluorescence in situ hybridization (FISH)?

Fluorescence In Situ Hybridization (FISH) is a technique that is used to detect chromosomal abnormalities in cells.

In CLL, FISH is used to analyze lymphocytes for chromosome defects. It is estimated that more than 50 percent of patients with CLL will have detectable chromosomal abnormalities, some of which are associated with disease progression and survival.

Examples of chromosomal abnormalities commonly found in CLL include, trisomy 12 and deletions in chromosomes 6, 11, 13, and 17. These are not the only chromosomal abnormalities that can occur in CLL, and combinations of abnormalities are also possible.

FISH can be performed on any number of specimens: tissue, bone marrow, peripheral blood, and fluids. It is usually performed on the specimen that is thought to harbor the cell line of interest. For most of the leukemias, the marrow is typically used, but other specimens that are sometimes evaluated include cells from the cerebrospinal fluid and the lymph nodes.

30. What does trisomy mean?

Cytogenetic tests are often carried out on leukemia patients to detect any chromosomal abnormalities associated with their disease. Trisomy is a chromosomal defect that involves the presence of an additional whole chromosome.

Every cell in the human body (with the exception of ovum and sperm) has 46 chromosomes. There are 22 pairs of chromosomes called somatic chromosomes plus the 2 sex chromosomes. As each cell prepares to undergo the usual process of cell reproduction (mitosis), it doubles the number of chromosomes and then splits into 2 cells, each with 46 chromosomes. Or at least that is how it is supposed to work.

Every now and again, three copies of a chromosome will go into one cell giving the cell a trisomy of a specific chromosome, and the remaining copy goes into the other cell resulting in a monosomy. Usually both of these circumstances result in the death of both

cells, but occasionally, a cell can live to produce a cell line that is unique, and unfortunately, unique cell lines can be malignant.

Trisomy 12, the presence of an additional 12th chromosome, is a trisomy that is frequently found in CLL patients. The defect responsible for trisomy 12 in CLL is not known. Studies suggest that CLL patients with such chromosomal abnormalities carry a poorer prognosis than patients with normal chromosomes.

We don't know exactly what causes these trisomies, and much more important, regardless of what the Human Genome project press releases say, we really don't know what information is where or what it means. So, all we can do at this stage is note that certain diseases seem to have certain trisomies, or monosomies.

31. What are some of the main prognostic indicators in CLL?

When a person has just been diagnosed with early stage CLL, it is important to exercise caution in making long-term predictions. The course of CLL is highly variable. Some patients remain without symptoms for years while in others the disease progresses much more rapidly. Only after a physician has had an opportunity to monitor a newly diagnosed, early stage patient for a period of approximately one year can a more reliable long-term prognosis be given.

A number of prognostic indicators are available to CLL patients and their physicians. Very few early stage patients will be tested for all of the indicators listed below, but they are some of the main indicators that are available. One should never rely on a single indicator, but should use as many of the indicators as possible in determining the prognosis. Most physicians experienced in treating individuals with CLL have developed their own set of indicators/tests that they use at different points in time after the initial diagnosis.

Newly diagnosed patients who are in early-stage disease will find these indicators particularly helpful in determining how their CLL might progress. Patients with more advanced disease will also find these indicators useful. These patients are often already aware of the indicators and their impact on prognosis.

Indicator	Prognostic implications
Lymphocyte doubling time	Peripheral lymphocyte doubling times of less than one year are indicative of aggressive CLL, whereas, doubling times of greater than one year suggest a more indolent situation.
Absolute lymphocyte count	Once an abnormal cell population is noted on a differential, the traditional method of reporting (the percentage) is no longer valid. Only the absolute counts correctly reflect the white cell population in the peripheral blood. The lymphocyte doubling can be seen here and together with the absolute granulocyte count, the general state of the individual's immune system can be seen. The absolute lymphocyte count is usually listed as either #LY or ABS LY on a differential report.
Hemoglobin level	Hemoglobin levels of greater than 13 grams per deciliter of blood (13g/dL) are desired. Levels of less than 13g/dL may

Diagnosis, Diagnostic Procedures & Other Tests

	indicate aggressive or advanced disease. Some laboratories report hemoglobin levels in liters and not in deciliters. In that situation the desired level is greater than 130 grams.
Bone marrow histology	Diffuse bone marrow involvement correlates with progressive or advanced disease, while nodular or interstitial (non-diffuse) patterns in the bone marrow indicate a better prognosis.
Beta-2-microglobulin	Beta-2-microglobulin (β 2m) is a piece of the cell membrane. When cells are particularly active or are damaged easily, this piece is broken off and remains in the plasma where it can be quantified. The slower the cell's activity or the less damage within the cell, the lower the amount of β 2m in the plasma. Patients with β 2m values below 2.0 mg/L seem to have a more favorable outlook than those with values above 2.0.
CD38 expression	Patients with less than 20 percent CD38+ CLL cells are likely to have a more favorable clinical course requiring minimal or no therapy, whereas, patients with greater than 20 percent CD38+ B-CLL cells are more likely to have an unfavorable clinical course requiring earlier and ongoing treatment. CD38 seems to be closely linked with IgV gene mutation; however, this correlation is a matter of debate.
Serum lactate dehydrogenase (LD or LDH)	Most cells in the body require this enzyme in their production of energy. As cells are damaged or die inappropriately, they will spill the contents of their cytoplasm into the peripheral blood where it can be quantified. There are five major types of LD and each can be identified through a procedure known as isoenzyme electrophoresis. Increases in LD can be seen when there is increased cell death due to chemotherapy or when a person is relapsing from remission.
Soluble CD23	CD23 is supposed to be found on all B-cells and a few other cells. B-cells are supposed to constitute less than 25% of the total number of lymphocytes in the peripheral blood. If CD23 levels begin to increase in the peripheral blood, it can be assumed that the number of B-cells in the blood stream is greater than expected (or wanted) in the blood stream.

Chromosome and gene abnormalities – normal chromosome profiles (karyotypes) are predictive of a more stable situation. However, chromosome abnormalities are found in a large percentage of CLL patients. Using molecular testing techniques, it is estimated that abnormalities can now be identified in approximately 80 percent of CLL cases. Prior to the availability of current molecular testing techniques, conventional testing detected abnormalities in 40 to 50 percent of cases. These abnormalities are helpful in predicting the course of CLL. Some of the most important disease-associated abnormalities and their implications for disease progression are shown below:

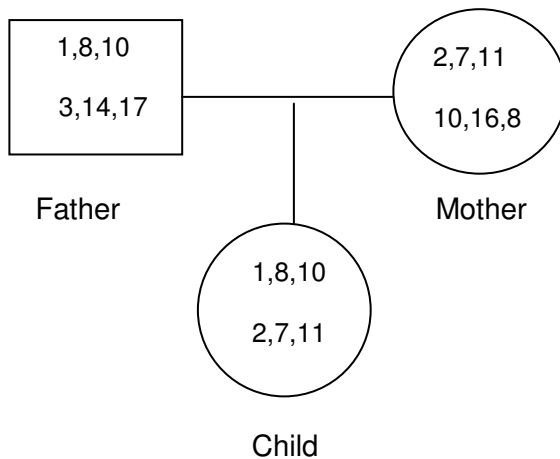
17p deletion	Aggressive disease progression.
11q deletion	Associated with a poor prognosis and often accompanied by bulky lymph node involvement. This deletion also identifies patients who are at high risk for disease persistence after high-dose therapy and autologous transplantation.
trisomy 12	Predictive of a shorter treatment free interval.
13q deletion	13q deletion is a positive indicator that predicts indolent disease progression.
p53 gene mutations	These mutations predict for non-response to treatment with alkylating agents and purine analogs.
p53 gene deletions	Patients with p53 deletions are thought to have a shorter survival time and to be more resistance to treatment than those without this deletion.
IgV gene mutation status	Unmutated IgV genes suggest an inferior prognosis; whereas, mutated IgV genes indicate a much better prognosis

Some patients will have combinations of these abnormalities. When looking at chromosomal abnormalities, it is also useful to consider the IgV gene mutational status. Patients with chromosomal abnormalities and mutated IgV genes have a better outlook than those with chromosomal abnormalities and unmutated IgV genes. Checking for IgV gene status is currently available only for research purposes. It is anticipated that it will soon be available in the clinical laboratory.

32. What is tissue typing?

Tissue typing is the name given to the test that identifies an individual's Human Leukocyte Antigens (HLA). HLA's are a set of six antigens that define "self". The concepts of "self" and "nonself" explain how lymphocytes tell the difference between what to attack and what to ignore. These antigens appear on the white blood cells as well as cells of almost all other tissues. They are analogous to red blood cell antigens, types A, B, O, etc. This test is used to match a blood or bone marrow donor to a recipient. By typing for HLA antigens, donors and recipients can be matched to ensure good performance and survival of transfused and transplanted cells. A perfect HLA match occurs only between identical twins.

HLA's are inherited from our parents, and it is therefore possible to determine which set was inherited from which parent (if tissue typing has been performed on both parents). The following example illustrates how HLA's are inherited:



Antigens are inherited from each parent as a group, and each set of antigens is called a haplotype. One haplotype must be inherited from each parent. Each number represents a separate inherited antigen. Other possible combinations arising from the parents above are, (1,8,10/10,16,8); (2,7,11/2,14,17); and (3,14,17/10,16,8).

Should two siblings have exactly the same HLA, it is referred to as an "identical match". Siblings who share one-half of the same HLA are referred to as a "one-haplotype match". Siblings who do not share any of the same HLA are referred to as a "two-haplotype mismatch". There are many Human Leukocyte Antigens in the general population, and for this reason, you may share HLA with someone who is not even related to you.

After tissue typing is completed and a potential donor is identified, a crossmatch test is performed to determine if there is specific immune reactivity between the donor and the recipient. If the patient has antibodies which react to the donor's HLA's, the donor's cells will be injured. This is referred to as a "positive crossmatch" and is a contraindication to transplant. A negative crossmatch indicates that the patient does not have antibodies against the donor's HLA, and a transplant can be performed. This type of crossmatch should not be confused with the traditional crossmatch used to test the compatibility of donor red blood cells and the patient's naturally occurring antibodies (e.g. anti-A, anti-B).

Lastly, a test called "antibody screening" determines whether or not the patient has antibodies to other Human Leukocyte Antigens. This enables the avoidance of those antigens when selecting an appropriate donor. Again, this antibody screening is not the only antibody screen that can be performed. For example, prior to any blood transfusion, a patient's blood will be tested to see if there are any unusual antibodies that would interfere with the donor red blood cells.

Integrating information from tissue typing, crossmatching, and antibody screening is extremely valuable in predicting compatibility between the recipient and the potential donor.

33. What is DiSC assay?

DiSC assay stands for Differential Staining Cytotoxicity. It is a technique that assesses the cytotoxic drug sensitivity of fresh human cells from patients with leukemia,

lymphoma, and other cancers. It is carried out outside the body (ex vivo) and has had most use with chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML or ANLL), and non-Hodgkin's lymphoma. Because individual differences in drug sensitivity are considerable, the DiSC assay attempts to assess how patients will respond to various chemotherapies prior to actually administering chemotherapy.

The center for DiSC assay research is Bath Cancer Research, Wolfson Centre, Royal United Hospital, Bath, BA1 3NG, England. The work is headed by Dr. Andrew G. Bosanquet, BSc, PhD, CBiol, MIBiol, CChem, FRSC. Bath Cancer Research provides an international service for consultant hematologists/oncologists, testing cells from patients for drug response against a panel of up to 35 cytotoxic drugs. Reports are then sent to consulting physicians to aid in the choice of optimum therapies. The information is intended to maximize the likelihood of response and reduce the risk of causing patient toxicity with no clinical benefit.

Critics of the DiSC assay procedure contend that cells do not necessarily react the same in the laboratory (in vitro) as they do in the body (in vivo). While there have been no comparative studies yet published that determine an increased efficacy of treatment based on this test, its proponents see it as a step toward tailor-made treatment.

Additional information on DiSC assay and Bath Cancer Research can be found on-line at <http://caltri.org>.

Treatment

34. Should I start treatment as soon as possible?

Patients with advanced stage CLL will likely start treatment immediately. However, early-stage patients are invariably given no treatment. Instead, they are monitored closely on three to six month intervals. This is one of the most difficult things for newly diagnosed, early-stage CLL patients to accept—the watch and wait approach that is taken to the management of early-stage CLL. People tend to think that they should start treatment as soon as possible in order to maximize their chances of recovery, as is the case with most cancers. CLL is exceptional in this particular respect.

The reason for the watch and wait approach is that CLL is generally thought to be incurable. Treatments are usually aimed at controlling the disease and managing its symptoms (palliative) not at curing the disease (curative). Over time, most treatments lose their efficacy, and for this reason, it is generally agreed that treatment should not begin until it is necessary to control the symptoms of the disease. Even escalating lymphocyte counts often do not mandate treatment.

35. What are the criteria for starting treatment?

Treat the symptoms, not the counts is an expression that is often used in the management of CLL. Indeed, the start of treatment is usually determined by a patient's symptoms. The types of symptoms that signal the start of treatment include, general lack of wellness, extreme fatigue, night sweats, low-grade fevers without any evidence of infection, significantly swollen lymph nodes, and frequent and recurrent infections. The aggressiveness of one's CLL along with their specific prognostic indicators will also be factors in selecting the time to begin treatment. Aggressive CLL will be treated sooner rather than later.

The decision to begin treatment is an important juncture in the CLL journey. As a general rule, one doesn't want to start treatment too early or wait too long. Selecting the right time to begin treatment and the type of treatment are very important decisions. Some patients prefer to leave these decisions entirely in the hands of their physicians, while others prefer to take an active role in determining both the timing and the selection of their treatments.

Following is a general outline of the types of treatments used in the various stages of CLL (see also: What are the stages of CLL?):

Stage 0 (elevated lymphocyte counts only) – Treatment is generally not needed.

Stage 1 (elevated lymphocyte counts and enlarged lymph nodes) – If the patient is without symptoms, treatment may still not be required. External radiation therapy to swollen lymph nodes and chemotherapy may also be considered.

Stage 2 (elevated lymphocytes, enlarged nodes, and liver or spleen enlargement) – If there are few or no symptoms, treatment may still not be required. Other possibilities at this stage include chemotherapy, external radiation to the spleen and/or lymph nodes, and clinical trials. (see also: What are clinical trials?)

Stage 3 (elevated lymphocytes and too few red blood cells; lymph nodes and liver or spleen may be enlarged) – Treatment at this stage may include any of the following: chemotherapy, external radiation to the spleen, surgery to remove the spleen (splenectomy), external radiation to the whole body (total body radiation), clinical trials of bone marrow transplantation, and clinical trials of biological therapy.

Stage 4 (elevated lymphocytes and too few platelets; lymph nodes, liver, or spleen may be enlarged, and there may be too few red blood cells) – The treatment options in stage 4 are much the same as stage 3.

Refractory CLL – Refractory means that the CLL initially or no longer responds favorably to treatment. The CLL may become refractory to a particular course of therapy in which case other therapies are used. If the CLL becomes refractory to all standard treatments, the patient's treatment options will depend on many factors. Two options that may be available to consider include entering a clinical trial of new chemotherapy, biological response modifier, or monoclonal antibody drugs and bone marrow transplantation.

36. How is CLL treated?

The main forms of treatment for CLL include the following:

Chemotherapy – drugs, taken either orally or intravenously, are used to kill cancer cells. Chemotherapy is called a systemic treatment because it enters the bloodstream and travels throughout the body.

Radiation therapy – x-rays or other high-energy rays are used to kill cancer cells and shrink tumors.

Biological therapy – a type of therapy that tries to get the body to fight CLL. It uses substances made by the body or made in a laboratory to boost, direct, or restore the body's natural defences against the disease. Biological therapy is also called biological response modifier (BRM) therapy or immunotherapy.

Surgery – in some cases, if the spleen is severely swollen and causing symptoms, it may be removed in an operation called a splenectomy.

Bone Marrow Transplantation (BMT) – there are two main types of bone marrow transplants: allogeneic and autologous. An allogeneic transplant uses healthy marrow taken from a donor whose tissue is the same as, or almost the same as, the patient's. Donors are classified as matched related donors or matched unrelated donors (MUD). An autologous transplant uses marrow from the patient, which has been treated with drugs to destroy any cancer cells. The treated marrow is then frozen and stored until the patient is ready for transplantation.

In bone marrow transplantation, all of the bone marrow in the body is destroyed with high doses of chemotherapy and radiation therapy. An exception is the non-myeloablative or mini-transplant (see also: What is a mini-transplant?). Healthy marrow, either from a donor (allogeneic) or from the patient (autologous) is then given to the patient intravenously to replace the marrow that was destroyed. Transplantation of bone marrow involves potentially serious risks, and patients require the care of skilled medical

staff and state-of-the-art support services. For this reason, BMT should be performed at established transplant centers wherever possible.

Supportive treatment – includes transfusion of packed red blood cells for anemia, platelet transfusions for bleeding associated with thrombocytopenia, and antibiotics for bacterial infections.

37. What drugs are used in treating CLL?

It is important for patients to understand the goals of treatment and to participate in treatment decisions. Treatment aimed at producing complete remissions will likely be different from treatment that is intended to manage symptoms and blood counts. Before embarking on treatment, be sure to understand the goals, the track record of the drugs being used, and their side effects.

Drugs used in treating CLL are administered either as single agent therapies or as combination therapies. Most physicians agree that complete remissions are more likely with combination therapies than with single agents. The rationale to combination therapy is to use drugs that work at different parts of the cell's metabolic processes, thereby increasing the likelihood that more cancer cells will be killed. In addition, the toxic side effects of chemotherapy may be reduced when drugs with different toxicities are combined; each at a lower dose than would be needed if one drug were used alone.

A number of drugs are used in the treatment of CLL. Following are examples of these drugs and the categories to which they belong. Where possible, the generic name is shown first followed, in parenthesis, by the trade name (capitalized) and any common names.

Alkylating agents – For many years, the standard first-line chemotherapy treatment for CLL has been the use of alkylating agents such as chlorambucil (Leukeran), cyclophosphamide (Cytosan), and busulfan (Myleran).

Corticosteroids – Corticosteroids, such as prednisone (Deltasone), are generally used in conjunction with other drugs such as chlorambucil. They have also been evaluated as single agent therapies. When used as single agents, decreases in node, liver, and spleen enlargement commonly occur, but complete responses are rare.

Purine analogues – Perhaps best known in this category is the drug fludarabine phosphate (Fludara, FAMP). Historically, fludarabine has been used primarily as a second-line therapy, after the initially used alkylating agent (chlorambucil or cyclophosphamide) stopped showing a satisfactory response. More recently, based on impressive test results, fludarabine has gained significant ground as a first line therapy, particularly in the US. Examples of other purine analogues used in the treatment of CLL are cladribine (Leustatin, 2-chlorodeoxyadenosine, 2CdA), pentostatin (Nipent, 2-deoxycoformycin), and compound 506U78 (AraG).

Antitumor antibiotics – These drugs are antibiotic chemotherapy agents, as opposed to antibiotics that work against bacteria. Antitumor chemotherapy agents in this category include drugs such as doxorubicin (Adriamycin) and mitoxantrone (Novantrone).

Monoclonal antibodies (Mab or MoAb) – Monoclonal antibodies are another method of treatment that, on theoretical grounds, promises to improve our ability to control CLL. One example is alemtuzumab (Campath-1H), an anti-CD52 monoclonal antibody that is toxic to all lymphocytes and which may be effective in producing remissions in patients who have failed prior therapies, including fludarabine. Another monoclonal antibody is rituximab (Rituxan, IDEC-C2B8), which is active against cells expressing CD20. Rituximab is also in clinical studies currently in conjunction with fludarabine and cyclophosphamide. Zevalin, a 90Y labelled anti-CD20 monoclonal antibody, is the radioactive form of rituximab. Tositumomabiodine (Bexxar) is another radioactive anti-CD20 monoclonal antibody. It is combined with radioactive iodine 131, which delivers lethal radioactivity to cancer cells and also flags them for destruction by the immune system.

Growth Factors and Cytokines – Growth factors are used to stimulate the production of different types of blood cells. Filgrastim (Neupogen, G-CSF), a granulocyte stimulating factor, epoetin alfa (Epogen, Procrit), a red cell stimulating factor, and thrombopoietin, a platelet stimulating factor are examples of growth factors.

The following table summarizes many of the drugs that are used in the treatment of CLL, some of which are still in clinical trials and not yet approved for general use:

Generic Name	Trade Name	Common Name	Type of Drug
aldesleukin	Proleukin	Interleukin 2	biological response modifier
alemtuzumab	Campath-1H	Campath-1H	monoclonal antibody
busulfan	Myleran	BSF	alkylating agent
chlorambucil	Leukeran	chlorambucil	alkylating agent
cisplatin	Platinol	cis-platinum	alkylating-like agent
cladribine	Leustatin	2CdA	purine antimetabolite
cyclophosphamide	Cytosan	CTX	alkylating agent
dexamethasone	Decadron	DXM	adrenal corticosteroid
doxorubicin	Adriamycin	hydroxydaunorubicin	antitumor antibiotic
epoetin alfa	Epogen, Procrit	erythropoietin	growth factor
filgrastim	Neupogen	G-CSF	growth factor
fludarabine phosphate	Fludara	FAMP	purine antimetabolite
mitoxantrone	Novantrone	DHAD	antitumor antibiotic

pentostatin	Nipent	2'-deoxycoformycin	purine antimetabolite
prednisone	Deltasone	prednisone	Corticosteroid
rituximab	Rituxan	IDEC-C2B8	monoclonal antibody
tositumomab	Bexxar	Iodine 131	investigational radioimmunotherapy
vincristine sulfate	Oncovin	vincristine	plant alkaloid

38. What questions should I ask prior to chemotherapy?

Following are some questions that patients may want to ask before beginning chemotherapy:

- What drugs will be used?
- What are the goals of this treatment?
- When will treatments begin? How often will they be administered? When will they end?
- Will they be administered on an outpatient basis?
- How will we know if the drugs are working?
- What side effects should I expect during treatment? How long do the side effects last? What can be done to manage them?
- Can these drugs cause side effects later on?
- Will they in any way affect or limit future treatment options?

39. What side effects should I expect from chemotherapy?

The side effects of chemotherapy depend mainly on the drugs being used, and as with other therapies, may vary from person to person.

Anticancer drugs generally affect dividing cells. Because cancer cells divide more often than healthy cells, they are more likely to be affected by chemotherapy. However, healthy cells that divide often may also be damaged by chemotherapy. Cells in this category include blood cells, cells in hair roots, and cells in the digestive tract.

When chemotherapy affects healthy cells, side effects may include, lowered resistance to infection, a tendency to bleed more easily, fatigue, nausea, loss of hair, vomiting, and mouth sores. Most side effects disappear gradually during the recovery periods between treatments or after treatment stops. Some anticancer drugs can also affect fertility, and these changes may be permanent. Patients are advised to ask about side effects prior to treatment. (see also: What questions should I ask prior to chemotherapy?)

40. Where in the CLL treatment plan does transplantation fit?

Bone marrow transplantation is a treatment approach that is applicable to only a subset of CLL patients. Until recently, CLL patients were generally not considered candidates

for bone marrow transplantation because of their age at presentation and the indolent nature of CLL. However, increasing consideration is being given to CLL patients with high-risk disease and poor prognostic factors such as, lymphocyte doubling time of less than 12 months, diffuse bone marrow infiltration, and adverse cytogenetics.

There are two main types of transplants. Autologous transplantation uses the patient's own bone marrow or stem cells. After the cells are removed from the patient, they may be treated in an attempt to remove leukemic cells—a process called purging—and are then given back to the patient. Allogeneic transplantation uses bone marrow or stem cells collected from a matched donor who may be related or unrelated to the patient.

The advantage of autologous transplantation is the opportunity to achieve remission without the risk of graft-versus-host disease (GVHD). Approximately eighty percent of autologous transplant patients achieve complete remissions. The disadvantage centers on the possibility that leukemic cells will be given back to the patient. The relapse rate with autologous transplantation is approximately 50 percent four years after transplant, and overall survival at the four year mark is between 50 and 80 percent. Unfortunately, there is no plateau in disease-free survival curves which, coupled with the high relapse rate, suggests that autologous transplantation does not cure CLL. Patients with disease that is sensitive to treatment and who are transplanted while in complete remission usually achieve the best outcomes.

Allogeneic transplantation offers the possibility of long-term control and perhaps even cure. Two types of allogeneic transplants are used in CLL: standard and non-myeloablative. The latter is the so-called mini transplant procedure. In both procedures, the donor cells given to the patient are totally free of leukemia. The disadvantage of allogeneic transplantation is that the donated cells may attack the patient's body, which is called graft-versus-host disease (GVHD). Ideally, the donor cells will come from a matched related donor—usually a sibling. If this is not possible, cells from a matched unrelated donor (MUD) can be used. Standard MUD transplants carry the greatest risk of all the transplant procedures with a three in ten chance the patient will die from the procedure itself. Treatment related mortality (TRM) in non-myeloablative transplants is somewhat lower. With allogeneic transplants the relapse rate ranges from 10 to 25 percent, and there is a plateau in disease-free survival curves, which suggests that a fraction of patients is cured with this procedure.

Transplant is usually considered only for patients with progressive disease who are running out of other treatment options and therefore have a poor prognosis. When the risk of CLL becomes greater than that of transplantation, the transplant option comes into consideration.

Age is also a factor when considering transplant. Younger patients tend to want, and are often able to better withstand, aggressive treatment. In some cases, aggressive treatment also seems to be more effective in younger patients. Older patients frequently don't want aggressive therapy, because they don't want to go through all of the potential side effects. The ability to rebound from high dosage chemotherapy also diminishes with age, and the risk of graft-versus-host disease is well established to increase with advancing years. As a rule of thumb, allogeneic transplantation becomes less of an option after a patient reaches 60 years of age, and autologous transplantation is usually ruled out after 65 years of age. However, it is important to note that there are some 65 year olds who are otherwise very fit and healthy and could be candidates for transplant,

while there are some 45 year olds who would not survive the procedure. The overall fitness of the patient is therefore somewhat of an overriding factor in determining the age-limit for transplant.

Transplant should not be considered or undertaken too early in the disease when the patient may have many more quality years of life with or without treatment. Similarly, it is important not to wait until the patient has already failed all other forms of treatment. In the latter situation, it is very difficult to perform a bone marrow transplant and achieve a good result. In summary, there is a window of time during the course of CLL when transplant makes the most sense to consider.

Patients who are considering transplant are encouraged to seek institutions and physicians that are performing this procedure in conjunction with CLL research. If this is not possible, patients are urged to find facilities that are experienced in transplants and have the skilled staff and state-of-the-art support services required to undertake this procedure.

41. Should early stage patients have stem cells harvested and stored for future autologous transplant?

Early stage CLL patients frequently wonder if, before the disease progresses any further, they should have stem cells removed (harvested) and stored for possible autologous transplantation in the future.

For autologous transplantation to be successful, the patient's marrow must be relatively free of disease when it is harvested. By the time CLL is diagnosed, the percentage of leukemic cells in the marrow is generally higher than is acceptable for the harvest procedure. For this reason stem cells are usually not harvested until after treatment begins and a remission is achieved. Some treatment centers feel that the best time to perform the harvest is at the first or second treatment induced remission.

The decision on whether or not to harvest and store cells will depend on several factors including the overall treatment strategy that has been agreed to with the patient and the ability to achieve a treatment induced remission that eliminates sufficient disease to perform the harvest procedure.

Another consideration is that most institutions doing bone marrow transplants do not have sufficient storage facilities for long-term cell storage, and that overrides all other considerations at many cancer centers.

42. What is a mini-transplant?

The mini-transplant, or transplant-lite as it is sometimes called, is a form of allogeneic transplant. Although it is commonly called a mini-transplant, the term used by physicians is, non-myeloablative transplant: myelo is a Greek word meaning marrow and ablate means to destroy. Thus, a non-myeloablative transplant is one that does not completely destroy the patient's diseased marrow. Because this procedure is relatively new—mid 1990's—it's risks and benefits have not yet been clearly established.

In a standard allogeneic transplant, the patient is given high-dose chemotherapy or radiotherapy or a combination of the two. The goal of this preparative regimen is to

totally destroy the patient's bone marrow in an attempt to eliminate all leukemic cells and to suppress the patient's immune system sufficiently to allow engraftment.

In a mini-transplant, however, the patient is given just enough chemotherapy to allow the donor's bone marrow or stem cells to engraft in the patient. If all goes as planned the T-cells from the donor will then recognize the patient's leukemic cells as foreign, and they will mount a response against the leukemic cells. This is called the graft-versus-leukemia effect.

The risks in a mini-transplant are certainly less than in a standard allogeneic transplant; however, the risk of developing chronic graft-versus-host disease is still very significant. For this reason, the mini-transplant is certainly not a minor undertaking as its name might suggest. Indeed, it should be viewed as potentially having the same frequency of long-term complications as a standard allogeneic transplant.

43. What is a peripheral blood stem cell transplant (PBSCT)?

Peripheral blood stem cell transplantation is similar to bone marrow transplantation. In the PBSCT procedure, healthy immature cells (stem cells) are removed from the patient's peripheral blood, instead of the bone marrow, and stored temporarily. The patient then receives high-dose chemotherapy and possibly radiation therapy to destroy leukemia cells, following which the stem cells are returned to the patient, where they can produce new blood cells to replace the cells destroyed by treatment.

44. What is a cord blood transplant?

Cord blood transplantation is a transplant technique that uses stem cells obtained from umbilical cord blood (UCB). The first successful cord blood transplant was performed in 1988, and since that time, cord blood transplantation has been performed with increasing frequency. Approximately 75 percent of cord blood transplants involve unrelated donors.

Umbilical cord blood transplantation (UCBT) has several potential advantages. Perhaps the main advantage is decreased incidence of graft-versus-host disease (GVHD), which is attributable to decreased functionality of fetal lymphocytes. This decreased functionality also enables transplants to be undertaken with a lesser degree of HLA matching. The use of cord blood also expands the size of the potential donor pool and enhances the speed of finding suitable matches. The potential for viral contamination such as cytomegalovirus is also sharply reduced, and the limitations of cross-racial matching can be largely overcome with UCBT.

Potential disadvantages of UCBT include possible transmission of genetic diseases that are clinically unapparent at birth. Maternal contamination of umbilical cord blood, while unlikely, is also a potential risk that could cause severe and even fatal graft-versus-host disease.

The availability of umbilical cord blood transplantation has raised many ethical questions that revolve around issues such as ownership, privacy, and allocation of limited resources. Patients who wish to learn more about the status and availability of umbilical cord blood transplantation are encouraged to discuss this possibility with their hematologists.

45. What is leukapheresis?

Leukapheresis is the removal of white blood cells (leukocytes) from the peripheral blood. The process requires access to veins in both arms. Blood is extracted from one arm into a machine that sorts out the various blood components according to their density and weight. White cells are removed, and the rest of the blood is returned to the patient via a needle in the other arm. The procedure usually takes 3-4 hours.

Leukapheresis can reduce the circulating white count rapidly, efficiently, and safely, in CLL patients. The question is whether such a procedure will provide the patient with short-term and/or long-term benefits. In a study of 59 CLL patients treated with therapeutic leukapheresis, reduction in elevated lymphocyte counts (lymphocytosis), swollen lymph nodes (lymphadenopathy), and swelling of the liver and spleen (hepatosplenomegaly) was noted in 50-60% of the patients studied.

Despite its ability to reduce circulating white counts, leukapheresis is not standard therapy for CLL. It is very expensive, and it usually has to be repeated every one to three weeks, or longer. Patients seeking additional information on the use of leukapheresis in the treatment of CLL should consult their hematologists.

46. What about alternative/complementary therapies?

At this time there are no proven complementary therapies for use in the treatment of CLL, and patients are advised to avoid herbal supplements like Echinacea that stimulate the immune system.

47. Is additional vitamin C recommended for people with CLL?

Vitamin C seems to stimulate lymphocyte activity, which is one of the reasons that Linus Pauling thought it was effective in the prevention of malignancy. However, when the malignancy is in the lymphocytes, it is not a good idea to stimulate them any further than already are.

We all need vitamin C to live. The question then is, what amount of vitamin C is appropriate for people with CLL? The consensus seems to be, stick with recommended daily allowances, and do not go too high above that.

48. What is a neutropenic diet?

Neutrophils are an important defense against infection, especially bacterial infection. Treatment and disease progression can both compromise neutrophil counts. When neutrophil counts fall below 1000 ($1.0 \times 10^9/L$), patients are in jeopardy of infections from bacteria found in everyday foods.

If neutrophil counts drop to near or below 1000, patients should be on a neutropenic diet and should be in close touch with their hematologists. Following are examples of foods that must be avoided when on a neutropenic diet:

- Raw nuts, vegetables, and salads
- Apples, peaches, grapes, plums, nectarines, kiwi, strawberries, and other uncooked thin-skinned fruits

- Self-serve buffets, salad bars, and deli foods
- Cheeses such as feta, brie, camembert, blue, etc.
- Raw or rare meats, fish, and poultry
- Commercially prepared potato or macaroni salad
- Raw, un-pasteurized milk and eggnog or milkshakes made with raw eggs
- Bakery breads, muffins, cakes donuts, and cream or custard filled cakes

In addition to the selection of appropriate foods, extra care is important in food preparation. Food preparers must wash their hands frequently in warm soapy water, especially if handling raw meat, chicken, eggs, and fish. Counter tops, cutting boards, and cooking utensils should also be washed with hot soapy water after they have come in contact with food.

Additional information on food preparation and foods that are safe for patients with neutropenia can be found on-line at <http://www.acor.org/leukemia/neutro.html>.

49. What medical centers specialize in treating CLL?

The following treatment centers are frequently mentioned in the treatment of CLL:

- Dana Farber Cancer Institute – Boston, Massachusetts (DFCI)
- Fred Hutchinson Cancer Research Center – Seattle, Washington (The Hutch)
- Johns Hopkins Medical Center – Baltimore, Maryland (JH)
- Long Island Jewish Hospital – New Hyde Park, New York
- Mayo Clinic – Rochester, Minnesota
- Memorial Sloan Kettering Cancer Center – New York, New York (MSKCC)
- M. D. Anderson Cancer Center – Houston, Texas (MDACC)
- Ohio State University Cancer Center – Columbus, Ohio
- Royal Marsden – London, England
- Stanford Medical Center – Stanford, California
- The Burnham Institute – La Jolla, California
- Thomas Jefferson University – Kimmel Cancer Institute – Philadelphia, PA
- University of California, San Diego – UCSD Cancer Center – La Jolla, California
- University of Michigan Cancer Center – Ann Arbor, Michigan
- Walter Reed Army Medical Center – Hematology/Oncology Service – Washington D.C.

A more complete list of cancer centers can be found at www.acor.org/leukemia.

50. What are clinical trials?

Clinical trials are treatment studies conducted with volunteers that help doctors to evaluate new treatments. Each trial is designed to answer specific scientific questions and to find better ways to prevent or treat disease. Patients who participate in such studies may have opportunities to receive treatments that have shown promise in research. Patients who take part in clinical trials make important contributions to medical science. Although these patients take certain risks, they may be among the first to benefit from improved treatment methods.

Patients who are considering participation in a clinical trial are encouraged to ask for a copy of the full protocol—the document that describes the clinical trial in detail. Consent

to participate in a trial should only be given after reviewing the full protocol and considering all other relevant clinical trials for which the patient might be eligible.

Most clinical research that involves the testing of new drugs progresses in an orderly series of steps. Cancer clinical trials generally follow three phases:

Phase I Trials - evaluate how a new drug should be administered (orally, intravenously, or by injection), how often, and in what dosage. A Phase I trial usually only enrolls a small number of patients.

Phase II Trials - provide preliminary information about how well the new drug works and generate more information about safety and benefit. Each Phase II study usually focuses on a particular type of cancer.

Phase III Trials - compare a promising new drug, combination of drugs, or procedure with the current standard. Phase III trials typically involve large numbers of people nation-wide. If you participate in a Phase III treatment trial, you are likely to be randomized (assigned by chance) to a group receiving either the new treatment or the standard treatment. The reason the clinical trial has been initiated is that the superiority of one treatment over the other has not yet been firmly established.

In the United States, one way to learn more about clinical trials is through PDQ, a computerized resource developed by the National Cancer Institute. PDQ contains information about cancer treatment and about clinical trials throughout the US. Cancer Information Service offices (1-800-4-CANCER) provide PDQ searches to callers and can tell physicians how to obtain regular access to the database. Information can also be found at <http://cancertrials.nci.nih.gov>. Another way to find out about clinical trials is to ask your hematologist how you can obtain information on trials in your area.

51. What constitutes a remission in CLL?

According to the National Cancer Institute-sponsored Working Group (NCI-WG) on Chronic Lymphocytic Leukemia, complete remission (CR) requires all of the following for a period of at least 2 months:

1. absence of enlarged lymph nodes
2. absence of enlarged spleen and liver
3. absence of constitutional symptoms
4. normal complete blood count (CBC) as exhibited by:
 - a) neutrophils greater than or equal to 1,500 per microliter of blood
 - b) platelets greater than 100,000 per microliter of blood
 - c) hemoglobin greater than 11 grams per 100 milliliters of blood (untransfused)
5. A bone marrow aspirate and biopsy should be performed 2 months after all of the above requirements have been met. The marrow sample must have less than 30% of nucleated cells that are lymphocytes, and lymphoid nodules should be absent. If the bone marrow is hypocellular, a repeat determination should be made in four weeks. Samples should be re-reviewed in conjunction with prior pathology.

A decrease in the absolute lymphocyte count is not considered in the response criteria for complete remission. Although this parameter may identify a therapy that has lymphocytotoxic activity, there is no evidence that it has long-term clinical implications.

A partial remission (PR) requires that the patient exhibit the following features for a period of at least two months:

1. a fifty percent or greater decrease in the peripheral lymphocyte count from the pretreatment baseline value
2. a fifty percent or greater reduction in lymphadenopathy and/or
3. a fifty percent or greater reduction in the size of the liver and/or spleen (if abnormal prior to therapy)

In addition to the factors outlined above, the patient must also exhibit one or more of the following:

4. Neutrophils greater than or equal to 1,500 per microliter of blood or a fifty percent improvement over the pre-treatment baseline
5. Platelets greater than 100,000 per microliter of blood or a fifty percent improvement over baseline
6. Hemoglobin greater than 11 grams per 100 milliliters of blood or a fifty percent improvement over baseline without transfusions.

52. What is minimal residual disease (MRD)?

Minimal residual disease (MRD) is the presence of residual CLL cells in a patient who has otherwise achieved a complete remission (CR) in accordance with National Cancer Institute (NCI) criteria.

When complete remissions are achieved, physicians can order a variety of tests for MRD using polymerase chain reaction (PCR) or flow cytometry. When minimal residual disease is present, it is predictive of a shorter event-free period of remission. For this reason, some physicians will attempt to intensify complete remissions by treating residual disease with drugs like rituximab (Rituxan) and alemtuzumab (Campath-1H).

Complete remissions with no evidence of minimal residual disease—sometimes called PCR negative—are thought to be the most durable CR's.

Related Disorders

53. Does CLL lead to other forms of cancer?

There is an increased risk of second and even third malignancies, which are attributed to failure of immune surveillance. Treatment-induced acute leukemias may also occur in a small percentage of patients. Transformation of CLL to diffuse large cell lymphoma (Richter's syndrome) is also a possibility.

54. What is the difference between CLL and lymphoma?

CLL and the other leukemias are primary disorders of the bone marrow, whereas, the lymphomas are malignant disorders that arise in the lymphoid tissue, most often showing up as solid tumors in nodes found throughout the body.

There are two broad groups of lymphomas: the non-Hodgkin's lymphomas (NHL) and Hodgkin's disease (Hodgkin's lymphoma). Like the leukemias, non-Hodgkin's and Hodgkin's lymphomas are categorized into several sub-types. Classification of the lymphomas is a controversial area that is undergoing evolution. Following is a modified version of the Revised European American Lymphoma (REAL) Classification:

Indolent Non-Hodgkin's Lymphomas

- Follicle center cell lymphoma, follicular
 - Grade I follicular small cleaved cell
 - Grade II follicular mixed
 - Diffuse small cleaved cell
- Diffuse small lymphocytic lymphoma
- Marginal zone lymphoma
 - MALT (extranodal)
 - Monocytoid B-cell lymphoma (nodal)
 - Splenic lymphoma with villous lymphocytes
- Mycosis fungoides/Sezary syndrome

Aggressive Non-Hodgkin's Lymphomas

- Diffuse large cell lymphoma (includes diffuse mixed cell, diffuse large cell, immunoblastic)
- Burkitt's lymphoma/diffuse small non cleaved cell lymphoma
- Lymphoblastic lymphoma
- CNS lymphoma
- Adult T-cell lymphoma
- Mantle cell lymphoma
- Post-transplantation lymphoproliferative disorder
- AIDS-related lymphoma
- True histiocytic lymphoma
- Primary effusion lymphoma

Hodgkin's Disease

- Lymphocyte predominance
- Nodular sclerosis
- Mixed cellularity
- Lymphocyte depletion

55. What is small lymphocytic lymphoma (SLL)?

Small lymphocytic lymphoma (SLL) is one of the subtypes of non-Hodgkin's lymphoma. Unlike the other lymphomas, SLL overlaps with CLL both clinically and morphologically.

Some practitioners consider SLL and CLL the same disease, differentiated only by how symptoms are presented in early stage disease. CLL shows up primarily in the bone marrow and peripheral blood, while SLL presents itself primarily in the lymph nodes or lymphoid tissues. Other practitioners see them as different diseases because of the different signs and symptoms that are associated with each. For example, a patient with SLL may complain of swollen nodes and of a low-grade fever while a patient with CLL might not have any complaints or a complaint of fatigue. A third group of practitioners visualizes these two diseases as the two ends of a straight line. They are connected and, as the disease progresses, come closer to each other, but they start out far apart.

56. What is hairy cell leukemia (HCL)?

Hairy Cell Leukemia is an uncommon form of chronic leukemia that, like CLL, affects B-lymphocytes. The median age at presentation of HCL is 55 years, and there is a 5 to 1 male predominance.

Most patients with HCL present with gradual onset of fatigue, others experience symptoms related to spleen enlargement, and yet others come to attention because of infections. Upon physical examination, an enlarged spleen (splenomegaly) is almost invariably present and may be massive. The liver is enlarged in approximately fifty percent of cases, but swollen lymph nodes are uncommon.

Laboratory findings include B-lymphocytes, which have characteristic "hair-like" projections when examined under the microscope and reduced numbers of all types of blood cells (pancytopenia). On immunophenotyping, the leukemic cells co-express the antigens Cd11c and CD22.

HCL is very responsive to treatment with cladribine (Leustatin, 2CdA) and pentostatin (Nipent, 2'-deoxycoformycin).

57. What is prolymphocytic leukemia (PLL)?

Prolymphocytic leukemia (PLL) is a rare variant of CLL. It is a related but distinct B-cell disorder and is one of the B-cell malignancies most often confused with CLL. Most PLL patients are diagnosed initially with PLL; however, some will have initially been diagnosed with CLL, which subsequently transforms and takes on the appearance of PLL.

Unlike CLL, the abnormal lymphocytes seen in PLL are immature cells (prolymphocytes), which are not normally seen in the peripheral blood. The diagnosis is PLL rather than CLL if more than half the leukemic cells are prolymphocytes. If there are prolymphocytes present, but they make up less than half of the abnormal cells, the condition is called mixed CLL/PL. A patient with PLL will typically have a very large spleen and a very high white blood count. Most patients do not have enlarged lymph nodes, but may have non-specific symptoms like tiredness and weight loss. PLL tends to be more aggressive than CLL and is less responsive to therapy. Approximately 10 percent of patients who have chronic lymphocytic leukemia will have their illness transform and take on the appearance of prolymphocytic leukemia. The condition T-cell PLL has no relationship to CLL or B-PLL.

58. What is Richter's syndrome?

Richter's syndrome is the transformation of CLL to diffuse large cell lymphoma, which is one of the non-Hodgkin's lymphomas. Laboratory tests usually confirm that the lymphoma originates from the same population of cells as the leukemia. In this case, it is considered a transformation. If the lymphoma arises from different cells, it can be regarded as a secondary cancer arising by chance.

Richter's syndrome is suspected in any CLL patient who shows the onset of otherwise unexplained fever, weight loss, increase in serum lactate dehydrogenase (LDH), localized enlargement of lymph nodes, and enlargement of the liver and spleen. In this situation, biopsy of the newly enlarged lymph nodes is indicated to determine whether or not lymphoma cells are present.

There are no obvious causes for the transformation of CLL to Richter's syndrome, which can affect patients at any stage of CLL, including those in complete remission. The incidence of Richter's transformation, which carries a poorer prognosis than CLL, has been reported at between three and ten percent.

59. What is mantle cell lymphoma (MCL), and is it related to CLL?

Mantle Cell Lymphoma (MCL) frequently comes up in the discussion of CLL because its clinical presentation is extremely similar to that of CLL. Enlarged liver and spleen (hepatosplenomegaly) and elevated lymphocyte counts (lymphocytosis) are common in both diseases. However, MCL is a non-Hodgkin's lymphoma, which has its origins in the lymph nodes, whereas CLL is a leukemia and has its origins in the bone marrow.

Flow cytometry results of MCL are very similar to those of CLL. CLL lymphocytes coexpress B-cell antigens CD19 and CD20 along with the T-cell antigen CD5. With the exception of SLL, MCL is the only disease that also expresses these antigens. However, CLL lymphocytes also express CD23; whereas, MCL lymphocytes do not. This lack of expression of CD23 is useful in distinguishing MCL from CLL. In addition, the antigen density of CD20 is typically much lower in CLL than it is in MCL. This is one of the reasons why rituxan, the anti-CD20 monoclonal antibody, is more effective in the treatment of lymphoma than it is in CLL. For more information on CD markers and flow cytometry see, [What is flow cytometry?](#)

MCL is also known as small-cleaved lymphoma, intermediate differentiation lymphoma, centrocytic lymphoma, and mantle zone lymphoma, but it should not be confused with

marginal zone lymphoma. MCL comprises approximately 5 percent of all non-Hodgkin's lymphomas. The median age at diagnosis is approximately 55 years and approximately 80 percent of patients are males. Three subtypes of MCL have been noted: Nodular MCL, Diffuse MCL and Blastic MCL. MCL, like CLL, is currently considered incurable.

60. Is there a connection between shingles and CLL?

Shingles is an infection caused by the varicella-zoster virus, which is the same herpes virus that causes chickenpox. Shingles occurs in people who have had chickenpox and is a reactivation of the dormant varicella-zoster virus. The disease generally affects the elderly, although it occasionally occurs in younger and/or immunodeficient individuals. CLL patients fall into the latter category, and for this reason, they are more prone to reactivation of the varicella-zoster virus. It is not possible to catch shingles from somebody who has it. A person can only get shingles by having chicken pox earlier in life. However, an adult with shingles can cause a person who has not had chicken pox to get chicken pox.

The first sign of shingles is usually a tingling feeling, itchiness, or stabbing pain on the skin. This progresses to a rash that appears as a band or patch of raised dots on the side of the trunk or on the face. The rash develops into small, fluid-filled blisters, which begin to dry out and crust over within several days. Shingles can be very painful and itchy but is not generally dangerous to healthy individuals. However, people with shingles on the upper half of the face should seek medical attention immediately as the virus may cause serious damage to the eyes. The rash and pain associated with shingles usually disappear within 3 to 5 weeks, although, the pain can persist much longer and be quite intense. The pain that continues after the rash from shingles has healed is called, postherpetic neuralgia (PHN).

Most people who have shingles have only one occurrence of the disease in their lifetimes; however, individuals with impaired immune systems may suffer repeated episodes. Treatment for shingles includes antiviral drugs such as acyclovir (Zovirax). The severity and duration of an attack can be significantly reduced by immediate treatment.

61. What is autoimmune hemolytic anemia (AIHA)?

Autoimmune hemolytic anemia (AIHA) is a form of anemia that is commonly associated with CLL. It is estimated that 10% to 20% of CLL patients may develop AIHA sometime during the course of their illness. The development of this condition does not have implications for the staging of CLL; rather, it is usually reported as a complication of progressing disease.

In AIHA, the immune system malfunctions and develops antibodies against the patient's own red blood cells and destroys them prematurely. Symptoms of AIHA include nosebleeds, bleeding gums, chills, fatigue, pallor, shortness of breath, rapid heart rate, jaundice, and swelling of the spleen (splenomegaly). Diagnosis is confirmed with a test called the direct antiglobulin test or Coombs test. The mainstay treatment of AIHA associated with CLL is prednisone. Some forms of AIHA are treated by splenectomy because the spleen destroys antibody-coated, red blood cells. Removing the spleen allows the antibody-coated cells to function longer.

AIHA is not the only form of anemia that occurs in CLL patients. Anemia can also occur as a result of chemotherapy, due to blood loss, and in advanced CLL when malignant lymphocytes compromise the production of normal blood cells. Other forms of anemia can also occur, but these are the most common reasons for anemia in CLL patients.

62. What is idiopathic thrombocytopenic purpura (ITP)?

Idiopathic Thrombocytopenic Purpura or Immune Thrombocytopenic Purpura is an autoimmune disease. These are a class of diseases where the body considers a normal part of itself foreign (in this case platelets), and it attacks the "foreign cells". In ITP, the platelets are "coated" by antibodies and the spleen recognizes this as something to be removed from circulation. As a result, these platelets are trapped in the spleen until they die and are recycled. The problem is that the body keeps making the antibody so a replacement generation of platelets also gets coated, and the cycle continues.

Thrombocytopenia means low platelets, and purpura refers to the purple looking bruises and spots that appear under the skin and mucous membranes (petechiae and ecchymoses). So, ITP is a bruising that is caused by low platelets, which are the result of an immune dysfunction.

Some cases of ITP are caused by drugs and others are associated with infection, pregnancy, or immune disorders. About half of all cases are classified as "idiopathic" meaning the cause is unknown. Approximately 2 – 4% of CLL patients develop ITP. It can occur at any stage of CLL.

The main symptom of ITP is bleeding which can include bruising and tiny red dots on the skin or mucous membranes. In some instances bleeding from the nose, gums, digestive or urinary tracts may also occur. ITP is often accompanied by fatigue and sometimes by depression.

ITP is characterized more by its description than the specific properties of the disease. It is the diagnosis when platelets are abnormally low and other diseases that can cause low platelets have been ruled out. The diagnosis of ITP is supported when a complete blood count and bone marrow biopsy or aspirate finds normal or increased platelet forming cells (megakaryocytes).

Treatment is based on symptoms. In some cases no treatment is needed. In most cases, corticosteroids, such as prednisone, are the first line of treatment because corticosteroids prevent antibody formation. Intravenous infusions of immunoglobulin (IVIg) may be used as the next line of treatment. Splenectomy is successful in about 75% of patients who have not responded to other therapy. While it may seem overly aggressive to remove the spleen, many people think that it is the spleen that is actually causing the problem through over zealous removal of the platelets. These platelets can and do work just as well as uncoated platelets, so removing the spleen allows them to live a "normal" lifespan and work as they should. Other drugs used with refractory ITP include cyclosporine, vincristine, danazol, and azathioprine (imuran).

63. What causes night sweats in CLL?

As CLL progresses, some patients will experience night sweats. It is important to advise your hematologist/oncologist if this occurs, as this is an indication that your CLL is progressing.

There are no clear-cut answers about why night sweats occur in CLL. There are some plausible explanations about metabolic dysfunction and changes in certain hormone levels (somewhat similar to the night sweats experienced by peri-menopausal women), but there are no clear-cut answers.

CLL-related night sweats are usually all over the body and often necessitate a change of bedding and nightclothes, whereas, menopausal night sweats tend to be less severe and are usually confined to the chest, neck, and head areas, and sometimes the bend of the elbow or knee.

Other
64. How will CLL affect my normal activities?

A 1998 survey of CLL list members asked about disruption of normal activities. Three hundred and forty list members responded as follows:

Years since diagnosis	Degree of disruption				
	None	Mild	Much	Total	
	%	%	%	#	%
Under 5	45.5	32.4	22.1	253	100
5 to 9.99	32.8	44.8	22.4	67	100
10 or more	40.0	45.0	15.0	20	100
Total	42.6	35.6	21.8	340	100

Seventy-eight to eighty-five percent of respondents said they experienced no or mild disruption in their lives. Especially interesting is that the time passed since diagnosis seems to make little difference.

The complete CLL List Survey can be found at www.acor.org/leukemia/survtoc.html. This excerpt is included in the CLL FAQ with permission of the copyright holders, Sheldon Messinger and Barbara Lackritz.

65. Should people with CLL stop donating blood?

Yes, because the bone marrow is already under stress and because of the possibility of passing on leukemic cells to someone else. The latter is thought to be unlikely, but it cannot be said with certainty that it is impossible.

66. What are some of the dental considerations in CLL?

Good dental hygiene is particularly important for CLL patients. The mouth is a source of bacteria, which can be a problem for patients with compromised immune systems.

Early stage CLL patients generally do not need to take special precautions other than regular brushing, flossing, check-ups, and cleanings. Patients with advanced disease should take added precautions. The use of anti-bacterial rinses is often recommended, as are antibiotics in conjunction with dental work and cleanings. Some dentists will pre-treat with antibiotics for cleaning and dental work. Patients are encouraged to ask their dentists about pre-medication prior to their visits.

Prior to chemotherapy, it is a good idea to have a dental check-up, cleaning, and any required dental work. During chemotherapy, as blood counts fall, patients must exercise caution in their normal brushing and flossing. Gums will bleed easily and sores in the

mouth often develop. This can set the stage for infections. Anti-bacterial rinses are helpful during this period and can be obtained through your dentist.

All patients should advise their dentists of their CLL. This is particularly important for patients with advanced stage CLL.

67. What are some of the terminal aspects of CLL?

Approximately one third of CLL patients will die from causes unrelated to their CLL. The majority, however, will die from CLL related causes. This question deals with some of the terminal aspects of CLL.

In many cases, patients live for several years without treatment and are able to carry on a normal lifestyle. In other cases, CLL may be much more aggressive. When symptoms of disease progression become apparent, treatment often alleviates symptoms through partial, and in some cases, complete remissions. As the disease progresses and becomes unresponsive to treatment (refractory), patients usually enter a terminal phase that can often last up to two years. During this terminal phase, there is considerable lack of wellness, both from the disease and from complications of therapy. Recurring hospitalization is not uncommon during this phase of CLL.

The most frequent causes of CLL-related death are, severe systemic infections such as, pneumonia and septicemia, bleeding, and severe wasting and weakness.

In a small number of cases, CLL will transform into diffuse large cell lymphoma (Richter's syndrome). In an equally small number of cases, CLL will transform into prolymphocytic leukemia. Both carry a poor prognosis, and there is no generally accepted, effective therapy for these terminal transformations. Physicians continue to study and evaluate treatment possibilities for this phase of CLL.

68. What should I tell children?

Children will pick up non-verbal signs that something is wrong and often they will imagine the worst. One of their worst fears is usually that of abandonment. For this reason, they need to be reassured that even though a parent is sick, there will always be someone available to take care of them.

Explain to them in very simple language that mommy or daddy has a disease called cancer. If you avoid the word, you are giving them the message that it is something too horrible to even talk about. Reassure them that the doctors are taking care of things and have medicines for treating the disease. If you know of expected side effects, prepare them in advance. It's important to be honest with them but to also keep it short and simple so as not to overwhelm them.

Invite them to come to you if they have any questions or worries. Although they need to feel that you are in control of the situation, it can be helpful to share some of your feelings, so they can see that it's safe to talk about their feelings. At some point, you may want to mention that nothing they did caused the illness and reassure them that the cancer is not contagious.

One of the questions children may ask is, are you going to die? With CLL a possible answer is, hopefully not for many years—after they are grown. It's also important to explain that people can die from leukemia. If children discover that we lied to them, they will have trouble trusting us again, and this will only create additional fears and insecurities for them.

69. What should I tell colleagues?

If there is no impact on your work, consider not disclosing until you need to and then only to those who need to know. Once you have a label in people's minds, it cannot be erased, and if people think you are going to be unable to carry your load, it will affect your work relationships.

70. How may I be in touch with other CLL patients?

For those who have access to the Internet, the CLL List is an on-line community of CLL patients, family and friends of patients, healthcare professionals, and others. Barbara Lackritz, a.k.a. GrannyBarb, founded the CLL List September 11, 1996, and as of April 2003 it has grown to over 2,106 subscribers in 33 countries. The List is a member of ACOR.Org, the Association of Cancer Online Resources, Inc., a 501©(3) non-profit corporation registered in New York State, and it is hosted on their Internet site at <http://listserv.acor.org>.

Subscribers are able to post messages to the List on a variety of topics including, questions and answers about symptoms, treatment information, complications, medical resources, hopes and fears, and general support. These postings are collected and mailed daily in digest form (single message) to all subscribers using robot software created by L-Soft International, Inc. The List is not moderated, so postings go directly to the List and are not screened by the List owners. People who prefer to receive individual posts may reset their subscriptions for that option. New members to the CLL family will experience a warm welcome and a strong sense of community and support on the CLL List.

The List has made a huge contribution toward exchanging and expanding knowledge about CLL. The archives are available to all List members. Come and join us on the CLL list. To subscribe, send an e-mail message to: listserv@listserv.acor.org. In the message of the e-mail, write: "Subscribe CLL" followed by your first and last names. Do not include any other information, or write anything in the subject line of the e-mail. If you use AOL, simply use a dash or a period in the subject line. On the web, visit <http://listserv.acor.org/SCRIPTS/WA-ACOR.EXE?SUBED1=cll&A=1>

Maggie Rice and Barbara Lackritz founded a Canadian CLL List (CLL-CN) November 2, 1999. The Canadian CLL List contains additional focus on issues facing Canadian CLL patients. Instructions for subscribing to the Canadian CLL List are almost the same as those for subscribing to the CLL List. The only change is in the message portion of the subscription e-mail where you must type, "Subscribe CLL-CN" followed by your first and last names. The Canadian CLL List has grown to 141 subscribers as of April 2003.

For information on local support groups, patients are encouraged to consult their hematologists or local chapters of the Cancer Society.

71. What are some of the leukemia-related organizations?

Chronic Lymphocytic Leukemia Foundation

The Foundation has as its main objective to fund research directed to finding a cure for Chronic Lymphocytic Leukemia (CLL). To this objective the Foundation seeks donations from individuals and organizations, disseminates information to increase public awareness of this illness and influence government policy towards a higher level of funding for research.

Address: 1415 Louisiana, Suite 3625
Houston, Texas 77002
Telephone: (713) 752-2350
Fax: (713) 752-2359

Internet: www.clfoundation.org

Leukaemia Research Fund (LRF)

The Leukaemia Research Fund (LRF) is the only national UK charity devoted exclusively to improving treatments, finding cures, and investigating the causes and prevention of cancers of the blood and related conditions, in children and adults. The LRF brings together under one banner scientists and doctors at leading hospitals, medical schools and universities across the UK to work towards its goal. LRF researchers are among world leaders in their fields.

More than 200 highly tuned research teams carry out the LRF's research. This includes 30 Specialist Programmes to develop key areas of research such as bone marrow transplantation and treating children with leukaemia.

A registered charity, the LRF relies on the dedicated support of more than 200 voluntary fundraising Branches and thousands of other people from all walks of life who contribute their time and money to make its work possible.

Address: 43 Great Ormond Street
London, WC1N 3JJ
Telephone: 020 7405 0101
Fax: 020 7405 3139

Internet: www.lrf.org.uk

Leukemia & Lymphoma Society, Inc.

The Leukemia & Lymphoma Society's mission is to cure leukemia, lymphoma, Hodgkin's disease, and multiple myeloma, and to improve the quality of life of patients and their families. The Society has dedicated itself to being one of the top rated voluntary health agencies in terms of dollars that directly fund this mission. Close to 80 percent of expenditures are directed to research, patient services, advocacy, education, and community services.

Address: Leukemia & Lymphoma Society, Inc.
1311 Mamaroneck Avenue
White Plains, NY 10605
Telephone: (914) 949-5213
Fax: (914) 949-6691

Internet: www.leukemia.org

Leukemia Research Fund of Canada

The Leukemia Research Fund of Canada is a volunteer driven organization whose mission is to eliminate leukemia and related blood diseases by funding vital Canadian research and promoting public understanding of the disease until the permanent cure is found.

Address: 1110 Finch Avenue West Suite 220
Toronto, Ontario M3J 2T2
Telephone: 1-800-268-2144
Fax: (416) 661-7799

Internet: www.leukemia.ca

Patient Databases, Inc.

PDI has been established to acquire data about symptoms, treatments, and medical tests relevant to blood diseases. The initial focus is on Chronic Lymphocytic Leukemia (CLL). PDI encourages all CLL patients to enter their medical and personal information so that data analysis can be performed on large numbers of patients, leading to potential discoveries about the relationships between age at diagnosis, gender, geographic location, time between treatments, rapidity of blood changes, the effectiveness of various treatments, and other factors. Much of the information collected will be based on the advice of medical and research specialists at the National Cancer Institute of the National Institutes of Health as well as international centers concerned with CLL. Results of analyses of the data will be made available to the medical community, public policy makers, patients and their families, and to the general public. PDI will also track additional data useful in diagnosis and the development of prognostic indicators for CLL. The potential usefulness of these approaches to other blood diseases and other chronic illnesses will also be explored in consultation with the scientific and medical community, advocacy groups, and others. The Board of Directors of PDI is comprised of patients and others who have an interest in finding a cure for chronic lymphocytic leukemia and other blood diseases, medical researchers and practitioners, public health specialists, information technology experts, and those concerned with increasing our knowledge of chronic lymphocytic leukemia and other blood diseases.

Address: 2005 37th Street NW
Washington, DC 20007
Telephone: (202) 337-2376
Fax: (202) 342-6434

Internet: www.patientdatabases.org

The CLL Research Consortium

The CLL Research Consortium is a multi-institution research program sponsored by the National Cancer Institute to study chronic lymphocytic leukemia (CLL) in an entirely new way. The CLL Research Consortium has its national coordinating office at the University of California, San Diego, School of Medicine.

The consortium is unique in that it brings together the nation's top scientists from different disciplines – genetics, cell biology, biochemistry, immunology and pharmacology – to conduct an integrated program of basic and clinical research focused on a single disease. CLL is the most common adult leukemia, and is currently incurable.

The member institutions are:

The Burnham Institute
La Jolla, CA

Ohio State University Cancer Center
Columbus, Ohio

Dana Farber Cancer Institute
Harvard Medical School
Boston, MA

Thomas Jefferson University
Kimmel Cancer Institute
Philadelphia, PA

Johns Hopkins University
Oncology Center
Baltimore, MD

University of California, San Diego (UCSD)
UCSD Cancer Center
La Jolla, CA

Long Island Jewish Medical Center
Division of Hematology/Oncology
New Hyde Park, NY

Walter Reed Army Medical Center
Hematology/Oncology Service
Washington, D.C.

M.D. Anderson Cancer Center
Houston, TX

Internet: <http://cll.ucsd.edu/index.htm>

Internet Links

This appendix includes a complete list of Internet links contained in the CLL FAQ.

- Association of Cancer On-Line Resources (ACOR): www.acor.org
- Bath Cancer Research (DiSC Assay): <http://caltri.org>
- Clinical trials: <http://cancertrials.nci.nih.gov>
- CLL specialist directory: <http://www.clloffoundation.org/DrDirectory.aspx>
- CLL Foundation: www.clloffoundation.org
- CLL List survey: www.acor.org/leukemia/survtoc.html
- CLL Medical News: www.acor.org/leukemia/medical_news.htm
- CLL Research Consortium: <http://cll.ucsd.edu/index.htm>
 - MD Anderson Cancer Center: <http://www.mdanderson.org/>
 - UCSD Cancer Center: <http://cancer.ucsd.edu/>
 - The Burnham Institute: <http://www.burnham.org/>
 - Dana Farber Cancer Institute: <http://www.cancercare.harvard.edu/>
 - Johns Hopkins University: <http://www.hopkinskimmelmccancercenter.org/>
 - Long Island Jewish Medical Center:
http://webhost.lij.edu/lijh/medicine/hematology_oncology/research.html
 - Ohio State University Cancer Center: <http://www.jamesline.com/>
 - Kimmel Cancer Institute: <http://www.kcc.tju.edu/>
- Frequently Asked Questions about Chronic Lymphocytic Leukemia (CLL FAQ): <http://cllfaq.acor.org>
- GrannyBarb's & Arts Leukemia Links: <http://www.acor.org/diseases/hematology/Leukemia/cll.html>
- HealthTalk Interactive: www.htinet.com
- Lab Tests Online: <http://www.labtestsonline.org/index.html>
- Leukemia Insights Newsletter: <http://www.mdanderson.org/publications/insights/>
- Leukaemia Research Fund (LRF): www.lrf.org.uk
- Leukemia & Lymphoma Society, Inc: www.leukemia.org
- Leukemia Research Fund of Canada: www.leukemia.ca
- National Cancer Institute: <http://www.nci.nih.gov/>
- Neutropenic diet: <http://www.acor.org/leukemia/neutro.html>

- Patient Databases, Inc: www.patientdatabases.org
- Susan's Posts (CLL postings by Dr. Susan Leclair):
<http://www.acor.org/leukemia/susan.htm>
- The Median Isn't the Message – An essay by Stephen J. Gould:
http://www.cancerguide.org/median_not_msg.html

Acronyms

The acronyms section of the CLL FAQ is included with permission of the copyright holder, Barbara Lackritz.

General Terminology

ALC	absolute lymphocyte count
ANC	absolute neutrophil count
BMB	bone marrow biopsy
BMT	bone marrow transplant (see specifics listed above)
B2M	beta 2 microglobulin test. Beta-2-microglobulin is a protein found on all the surface of all cells and small amounts are shed into the serum. People diagnosed with blood diseases and who have levels of beta-2-microglobulin below 2.0 seem to have a longer survival rate.
Bx	biopsy
B/P	blood Pressure
CBC	complete blood count
CCDRT	cell culture drug resistance testing
CD	cluster of differentiation
Cnet	Cancernet (where one gets PDQ and Cancer Lit papers)
CR	complete remission
CRN	complete remission with nodular pattern in marrow
CS	clinical Stage
DLI	donor lymphocyte infusion
Dx	diagnosis
EORTC	European Organization for Research and Treatment of Cancer
FISH	Fluorescence In Situ Hybridization. It is a test used to detect chromosome abnormalities in cells and has been used to test lymphocytes in CLL. The results help to predict the prognosis for a particular patient.
GP	General Practitioner: Doctor within NHS (UK)
GVHD	graft versus host disease
GVL	graft versus leukemia or graft versus lymphoma
HCT	hematocrit—the percentage of red blood cells in the blood. A low hematocrit measurement indicates anemia.
HDC	high dose chemotherapy--often used to condition one before a BMT or PBSCT
Hem/Onc	hematologist/oncologist
HGB	hemoglobin
HLA	Human leukocyte antigen test. A special blood test used to match a blood or bone marrow donor to a recipient for transfusion or transplant.
Ig	Immunoglobulin (IgA, IgD, IgE, IgG, IgM)
IV	intravenous—into a vein
Mab or MoAb	monoclonal antibodies (i.e. Campath-1H, Rituxan, Bexxar)
MCV	mean corpuscular volume
MCHC	mean corpuscular hemoglobin concentration
MCH	mean corpuscular hemoglobin

MD	Medical Doctor (USA)
MLUS	monoclonal lymphocytosis of undetermined significance
MRD	minimal residual disease
MUD	matched unrelated donor of bone marrow
NMDP	National Marrow Donor Program --1-800-526-7809
NR	nodular remission (nodules of cancer cells remain in the marrow, but there are less than 10% cancer cells throughout)
OR	overall remission
PCP	primary care physician
PCR	polymerase chain reaction
PDQ	physicians data query
PHN	postherpetic neuralgia
PR	partial remission
RBC	red blood count
RDW	red cell distribution width
RX	prescribed medication
SWOG	Southwest Oncology Group
TBI	Total body irradiation
TRM	treatment-related mortality
WBC	white blood count
WBC/HPF	white blood cells counted per high powered field
WD	well differentiated
WW	watch and wait (also called, watch and worry)
XRT	external radiation therapy

Diseases

AA	aplastic anemia
AIHA	autoimmune hemolytic anemia
ALL	acute lymphocytic leukemia (+3 subtypes according to morphology. L1-L3 and subtypes according to phenotype: T, pre-B, pre-pre-B, B)
AML	acute myelogenous leukemia (+8 subtypes MO-M6)
AMM	agnogenic myeloid metaplasia
AMML	acute myelogenous leukemia
ANLL	acute non-lymphocytic leukemia (same as AML above)
APL	acute promyelocytic leukemia
APML	acute promyelocytic leukemia
BCP-ALL	B-cell precursor acute lymphoblastic leukemia
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia (each has subtypes)
CMML	chronic myelomonocytic leukemia
CNSL	central nervous system lymphoma
ET	essential thrombocythemia
HCL	hairy cell leukemia
HD	Hodgkins lymphoma (4 subtypes)
ITP	idiopathic thrombocytopenic purpura
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome (4 subtypes)
MF	mycosis fungoides (cutaneous T-cell lymphoma)
MM	multiple myeloma

MPD	myeloproliferative disorders
NHL	non-Hodgkins lymphoma (many subtypes)
PLL	prolymphocytic leukemia
PV	polycythemia vera
SLL	small lymphocytic lymphoma
SLVL	splenic lymphoma with villous lymphocytes
WM	Waldenstrom's Macroglobulinemia

Treatment Options

ABMT	autologous bone marrow transplant—your own marrow
BMT	allogeneic bone marrow transplant—someone else's marrow
PBPC	peripheral blood progenitor cell transplant (which is becoming the new standard term)
PBSCT	peripheral blood stem cell transplant
PBSCR	peripheral blood stem cell rescue
PSCT or PSCR	The same as above without the word "blood."
SBMT	syngeneic bone marrow transplant—identical twin's marrow

Chemotherapies

ABVD	doxorubicin, vinblastine, bleomycin, DTIC
ACOB	doxorubicin, cyclophosphamide, vincristine, bleomycin
ARA-C	cytarabine
ATRA	all-trans retinoic acid, or Vesanoid
BACOP	bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone
BEAM	busulfan, etoposid, ara-c, melphalan
BLEO	bleomycin
2CdA	2-chlorodeoxyadenosine (Generic name = cladribine)
C-MOPP	cyclophosphamide, oncovin, procarbazine, prednisone
CCNU	(1-2-chloroethyl)-3-cyclohexyl-1-nitrosourea)
CHOD	cyclophosphamide, doxorubicin, vincristine, dexamethasone
CHOP	cyclophosphamide, adriamycin, vincristine, prednisone
CHOP-BLEO	cyclophosphamide, doxorubicin, vincristine, prednisone and bleomycin
CMF	cyclophosphamide, methotrexate, fluorouacil
COP	cyclophosphamide, oncovin, prednisone
COPP	CCNU, vincristine, procarbazine, prednisone
CyA	cyclosporin A
CVP	cyclophosphamide, vincristine, prednisone
DCF	2-deoxycoformycin (pentostatin)
DTIC	dacarbazine, 5-(3,3-dimethyl-1-triazino)imidazole-4- carboxamide
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide (cytoxan), adriamycin
ESHAP	etoposide (VP-16), methylprednisolone (SOL), cytarabine (AraC), cisplatin (CDDP) and prednisone (Pred).
FAC	fluorouacil, adriamycin, cyclophosphamide
FCR	fludarabine, cyclophosphamide, rituxan

Flu	fludarabine (Fludara)
IFN	Interferon (comes in alpha2a, alpha 2b, human leukocyte, and beta--Another one "consensus" is still in trials)
IL	Interleuken
mBACOD	methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone
MOPP	nitrogen mustard, vincristine, procarbazine, prednisone
MTX or M	methotrexate
proMACE	prednisone, methotrexate with leukovorin rescue, doxorubicin, cyclophosphamide, etoposide (VP-16)
RFC	rituximab, fludarabine, cyclophosphamide

Blood Stimulating Factors

EPOIETIN	erythropoietin (Epogen)-- is used to stimulate red cell growth.
G-CSF	granulocyte colony stimulating factor (Neupogen)- stimulates growth of white cells .
GM-CSF	granulocyte macrophage - colony stimulating factor (sargramostim)
NEUMEGA	platelet stimulating factor
TPOIETIN	thrombopoietin - (platelet stimulating factor)

Frequently-Mentioned BMT Centers

ACRC	Arkansas Cancer Research Center
Brigham	Brigham and Women's Hospital, Boston, MA
DFCI	Dana Farber Cancer Institute, Boston, MA
FHCRC or the Hutch	Fred Hutchinson Cancer Research Center, Seattle, WA
JH	Johns Hopkins Medical Center, Baltimore, MD
MDACC	MD Anderson Cancer Center, Houston, TX
MSK or MSKCC	Memorial Sloan-Kettering Cancer Center, NYC, NY
NCI	National Cancer Institute, Bethesda, MD
Roswell	Roswell Park Cancer Center in Buffalo, NY
Strong	Strong Memorial Cancer Center at Univ. of Rochester, NY

see: <http://www.acor.org/leukemia/canctrs.html> for others

Institutions

ACOR	Association of Cancer Online Resources
CIS	cancer information service (of NCI) 1-800-4-CANCER
CLL Found	CLL Foundation to raise funds for CLL Research
FDA	Food and Drug Administration (USA)
NCI	National Cancer Institute (USA)
NIH	National Institutes of Health
LRF	Leukaemia Research Fund (UK)
LSA	Leukemia Society of America (USA)
NHS	National Health Service (UK)

Glossary of Terms

Absolute lymphocytosis: The presence of more than 15,000 lymphocytes in a cubic millimetre of blood.

Acute: Sudden onset of disease symptoms.

Acute lymphocytic leukemia (ALL): The most common type of leukemia in young children. This disease also affects adults; especially those age 65 and older. ALL is characterized by the unrestrained production of immature lymphoblasts and has three subgroups, L1 to L3.

Acute myeloid leukemia (AML): AML occurs in both adults and children. This type of leukemia is also known as acute myelogenous leukemia and acute nonlymphocytic leukemia (ANLL). AML is characterized by a massive proliferation of mature and immature, abnormal granulocytes. There are eight subgroups of AML which are designated M0 to M7.

Adenopathy: Swelling or morbid enlargement of the lymph nodes.

Alkylating agents: Anticancer drugs that can damage DNA of cells, leading to cell death.

Allogeneic bone marrow transplantation: A procedure in which a patient receives bone marrow from a compatible, though not genetically identical donor.

Alopecia: Loss of hair, be it on the head or all over the body. Alopecia can be caused by certain chemotherapy drugs.

Anecdotal: A single case report not yet substantiated by clinical trials or studies using large numbers of people.

Anemia: A below-normal number of red blood cells.

Angiogenesis: Development of blood vessels.

Anthracyclines: Drugs used in leukemia therapy to prevent cell division by disrupting the DNA. Drugs of this type include, daunorubicin, doxorubicin (adriamycin), epirubicin, and idarubicin.

Antibodies: Proteins produced by certain white blood cells in response to the presence of foreign substances (antigens). Each antibody can bind to only one specific antigen. The purpose of this binding is to help destroy that antigen.

Antigen: Any substance that the body regards as foreign. When introduced into the body, an antigen causes the immune system to produce a corresponding antibody to fight it.

Antimicrobial therapy: Treatment to kill micro-organisms (such as bacteria or fungi) or to suppress their growth.

Apheresis: Removal of blood from the body using specialized equipment and single-use tubing in order to extract various blood cell types such as, platelets, white blood cells, stem cells, etc. After these cells are extracted, the remaining blood is returned to the body.

Aplasia: Failure of the bone marrow to produce blood cells. Usually this condition affects all types of blood cells, which is called aplastic anemia.

Aplastic anemia: A form of anemia that occurs when the bone marrow fails to produce adequate numbers of blood cells.

Apoptosis: Programmed cell death. If apoptosis is affected, the cell will not die, causing a malignant or cancerous condition.

Aspirate: To remove material from a body cavity by suction through a needle. Also refers to material that is removed this way.

Asymptomatic: Without symptoms.

Autoimmune disease: Diseases caused by an individual's immune system producing antibodies against tissues of its own body.

Autologous bone marrow transplantation: A procedure in which bone marrow that has been removed from the patient is given back to the patient. The marrow may be purged in the laboratory in an effort to eliminate contamination with leukemia cells. This procedure may be carried out up to the age of 55 - 60 years.

Axillary lymph node: A lymph node found in the armpit (axilla).

B-cells: (bone marrow derived cells) White blood cells, also known as B-lymphocytes, that develop in the bone marrow and are capable of producing antibodies.

Basophil: A type of white blood cell. Basophils are one type of granulocyte.

Biological response modifier (BRM): A substance that boosts, directs, or restores the body's normal immune (defense) system. An example is interferon. BRM's are produced naturally in the body and can also be manufactured in the laboratory.

Blast cells: Immature blood-forming cells which normally represent up to 5 percent of the cells in the bone marrow.

Blood-brain barrier: A network of blood vessels located around the central nervous system with very closely spaced cells that make it difficult for potentially toxic substances—including anticancer drugs—to penetrate the blood vessel walls and enter the spinal cord.

Bone marrow: The soft, spongy tissue in the center of many bones; it produces white blood cells, red blood cells and platelets.

Bone marrow aspiration: The removal of a sample of fluid and cells from the bone marrow for examination under a microscope. Aspiration is done with a needle. The results of the examination tell the doctor whether cancer cells are present.

Bone marrow biopsy: The removal of a sample of solid tissue from the bone marrow for examination under a microscope. The results of the examination tell the doctor whether cancer cells are present.

Bone marrow harvest: The removal and collection of bone marrow, usually done prior to a bone marrow transplant but sometimes done as a preventive measure in case of relapse.

Bone marrow suppression: A decrease in the number of blood cells produced which may be a result of treatment or tumor invasion of the bone marrow.

Bone marrow transplantation (BMT): A procedure in which doctors replace marrow destroyed by high doses of anticancer drugs and/or radiation.

Bulky disease: Any cancerous lymph node or extranodal tissue that measures greater than 10 centimeters in any dimension. The term bulky disease is often found in literature on the leukemias.

Cancer: A term for diseases in which abnormal cells divide without control.

Candida: A type of fungus. Candida infection in the mouth (oral thrush) is a common problem for immunosuppressed patients.

Carcinogen: A substance or agent that produces cancer.

Cell: The smallest living unit of tissue, composed of a nucleus and cytoplasm surrounded by a membrane. The nucleus houses DNA, and the cytoplasm contains structures (organelles) that carry out the cell's functions.

Cell surface marker: An identifying substance on the surface of cells.

Central nervous system (CNS): The brain and the spinal cord.

Cervical lymph node: A lymph node found in the neck.

Chimeric antibody: An antibody that is made of both mouse and human antibodies, usually a 30/70 percent split, respectively.

Chemotherapy: Treatment using anti-cancer drugs, which may be used singly or in combination to kill or prevent the growth and division of cells. Chemotherapy will also unavoidably affect rapidly dividing normal cells such as in the hair and the stomach causing hair loss and nausea. These side effects are usually temporary and reversible.

Chromosome: A structure in the nucleus of a cell containing DNA, which transmits genetic information. Normally, 46 chromosomes appear as a long thread inside each human cell.

Chronic: Lasting for a long period of time or marked by frequent recurrence.

Chronic lymphocytic leukemia (CLL): A form of leukemia that often progresses slowly and is characterized by the relentless accumulation of lymphocytes. CLL is the most common form of leukemia in the western world and most often affects adults over the age of 55. CLL sometimes occurs in younger adults, but it almost never affects children.

Chronic myeloid leukemia (CML): A form of leukemia that usually progresses slowly and is characterized by increased production of granulocytes in the bone marrow. CML occurs mainly in adults, although, a very small number of children also develop this disease. CML is usually associated with a specific chromosome abnormality called the Philadelphia chromosome.

Clinical trial: Medical research conducted with volunteers. Each trial is designed to answer scientific questions and to find better ways to prevent or treat disease.

Clone: A population of genetically identical cells arising from a single parent cell. Leukemia cells originate from one abnormal cell producing a "leukemic clone".

Clotting episodes: The inappropriate development of blood clots due to disease.

Cluster of differentiation (CD): Antigen markers found on lymphocytes that are used to determine the function of the cell. Each cell has only one kind of antigen.

Colony-stimulating factors (CSF's): Proteins that stimulate the development of cells in the bone marrow.

Committed cells: Cells that have matured sufficiently that microscopic examination can reveal what type of cell they will be when fully matured.

Comorbidity: An illness one has in addition to cancer.

Complementary therapy: Techniques or approaches often used in addition to standard treatment. Examples are diet and meditation.

Complete blood count (CBC): Measurement of the numbers of white cells, red cells, and platelets in a cubic millimetre of blood.

Complete remission (CR): The disappearance of all signs and symptoms of disease.

Computer assisted tomography (CAT Scan or CT Scan): A sophisticated x-ray technique used to produce detailed internal images of the body, particularly the chest and abdomen.

Conditioning: Treatment with high-dose chemotherapy, and sometimes with high-dose radiation therapy, to prepare a patient for bone marrow transplantation or peripheral blood stem cell transplantation.

Congenital: Present at birth.

Consolidation therapy: Chemotherapy or radiotherapy that frequently follows induction therapy, and which is intended to destroy all remaining cancer cells.

Corticosteroids: Complex chemical compounds produced in the outer layer of the adrenal gland, which is located near the kidney. They are important in regulating body chemistry. Corticosteroids can be manufactured in the laboratory and used as drugs.

Cross-matching: A test for incompatibility between donor and recipient blood.

Cytogenetics: The study of the structure of chromosomes. Cytogenetic tests are carried out on leukemia patients to detect any chromosomal abnormalities associated with the disease. This helps in diagnosis and selection of optimal treatment.

Cytokines: Hormones or growth factors produced by cells that help regulate cell processes.

Cytomegalovirus (CMV): A virus that is harmless in healthy people but may cause serious disease in severely immunosuppressed patients. CMV is a member of the herpes family of viruses and may manifest itself as pneumonia, colitis, or hepatitis. It is particularly dangerous following a bone marrow transplant.

Cytoplasm: The fluid, liquid, or “watery” part of a cell; the cytoplasm surrounds the nucleus of the cell.

-cytosis: A suffix which indicates an abnormally high number of blood cells. Examples include, lymphocytosis, erythrocytosis, and thrombocytosis.

Cytotoxic: Anything that kills cells. Many cancer treatments are cytotoxic to both healthy and cancerous cells.

Deletion: Loss of a piece of DNA from a chromosome. Deletion of a gene or part of a gene can lead to disease or abnormality.

Differential white blood count: An estimate of the percentage of white blood cell types which make up the total white blood count.

Differentiation: The process in which cells mature and become specialized.

DNA: Deoxyribonucleic acid; nucleic acid is present in all living cells. DNA contains the genetic information of the cell.

Ecchymoses: Purplish patches caused by extravasation of blood into the skin. Differing from petechiae only in size.

Endemic: Constantly present in a population.

Engraftment: The process in which transplanted bone marrow or peripheral blood stem cells begin to grow in the bone marrow of the host and to manufacture new white blood cells, red blood cells, and platelets.

Enzyme: A protein molecule that is a catalyst for chemical reactions of other substances and which is unaltered when reactions are complete. Enzymes are divided into six main groups.

Eosinophil: A type of white blood cell. Eosinophils are one type of granulocyte.

Epidemiology: The study of the factors that determine how diseases are distributed in a community.

Erythrocytes: Red blood cells.

Etiology: The cause of a disease.

Extravasation: To exude or pass out of a vessel into the surrounding tissues—said of blood, lymph, or urine. Can also apply to chemotherapy agents that are administered intravenously.

Fibrous: Containing fibres (threadlike noncellular structures). When bone marrow becomes fibrotic, it can be difficult to obtain a bone marrow sample.

Five-year survival rate: The percentage of people with a given cancer who are expected to survive five years or longer with the disease. Five-year survival rates, while statistically valid, should not be seen as a predictor in individual cases.

Flow cytometry: A diagnostic technique that is used to measure the chemical or physical characteristics of cells in suspension.

Fluorescence in situ hybridization (FISH): A process which vividly paints chromosomes or portions of chromosomes with fluorescent molecules. This technique is useful for identifying chromosomal abnormalities and gene mapping.

Frequency: The number of times a wave pattern repeats.

Genetic: Inherited; having to do with information that is passed from parents to their children through DNA.

Graft: Tissue taken from one person (donor) and transferred to another person (recipient) or taken from one part of a person's body and transferred to another part of the same person's body.

Graft-versus-host disease (GVHD): A condition that may develop after allogeneic bone marrow transplantation; the transplanted marrow (graft) attacks the patient's (host's) organs.

Graft-versus-leukemia (GVL): A reaction of donated bone marrow or peripheral stem cells against a patient's own leukemia cells.

Granulocyte: A type of white blood cell. Neutrophils, eosinophils, and basophils are granulocytes.

Granulocyte colony-stimulating factor (G-CSF): A growth factor that promotes the production and development of granulocytes.

Group C status: A designation for investigational anticancer drugs that are effective against one or more forms of cancer but have not been approved for general marketing by the U.S. Food and Drug Administration. Doctors may obtain Group C drugs from the National Cancer Institute to treat patients who would benefit from their use.

Hairy cell leukemia (HCL): A rare form of leukemia related to chronic lymphocytic leukemia and characterized by the presence of abnormal cells with hair-like projections.

Hematocrit: The percentage of blood that consists of red blood cells. Sometimes expressed as packed cell volume (PCV).

Hematologist: A doctor who specializes in studying and treating diseases of the blood.

Hematology: The study of blood, blood producing organs, and blood disorders.

Hematoma: A localized mass of blood that has passed out of a blood vessel and into the tissues.

Hematopoiesis: The formation and development of blood cells.

Hemoglobin: The protein found in red blood cells that carries oxygen. Hemoglobin gives blood its red colour.

Hemorrhagic cystitis: Bleeding from the bladder, which can be a side effect of the drug cyclophosphamide.

Hepatomegaly: Enlargement of the liver.

Hepatosplenomegaly: Enlargement of the liver and spleen.

Heterogeneous: Composed of parts having various and dissimilar characteristics or properties.

Histocompatibility: The degree of tissue similarity between the donor and recipient that will determine how easily the donor cells will be accepted and/or the likelihood and severity of graft-versus-host disease (GVHD).

Histology: The study of the microscopic structure of cells.

Hodgkin's disease: A malignant disease of the lymph nodes characterized by painless enlargement of lymphatic tissues and the spleen. Symptoms often include fever, weight loss, anemia, and night sweats. Named for the doctor who first identified it.

Host: In the case of an organ or bone marrow transplantation, the recipient of the organ or marrow.

Human leukocyte antigens (HLAs): A set of six antigens used to match a blood or bone marrow donor to a recipient. These antigens appear on white blood cells as well

as cells of almost all other tissues and are analogous to red blood cell antigens (type A, B, O, etc.). By typing for HLA antigens, donors and recipients of white blood cells, platelets, and organs can be matched to ensure good performance and survival of transfused and transplanted cells. A perfect HLA match occurs only between identical twins.

Idiopathic: Having no known cause.

Idiopathic thrombocytopenic purpura (ITP): Also known as immune thrombocytopenic purpura. ITP is classified as an autoimmune disease. It is a rare disorder characterized by an acute shortage of platelets with resultant bruising and spontaneous bleeding. Anti-platelet antibodies are detectable in some cases. It may be present in either an acute or a chronic form.

Immune response: The activity of the immune system against foreign substances (antigens).

Immunoglobulin: A specific protein substance that is produced by plasma cells to aid in fighting infection. Examples include IgG, IgM, IgA, IgD and IgE.

Immunoglobulin therapy: Treatment with antibodies to prevent infection.

Immunophenotyping: Determining what kind of surface molecules are present on cells. Used by pathologists to determine the exact type of leukemia from a blood sample.

Immunosuppressant: A drug (such as chemotherapy) or other factor that prevents the immune system from reacting to foreign substances and fighting disease.

Immunosuppression: Suppression of the immune response as a result of drugs (chemotherapy) or radiation.

Immunotherapy: Treatment of disease by inducing, enhancing, or suppressing an immune response.

Incidence: The number of new cases of a specific disease occurring during a given time period.

Indolent: Characterized by slow progression—a disease process or a tumor of low malignancy.

Induction therapy: Chemotherapy or radiotherapy intended to induce a remission.

Inguinal lymph node: A lymph node found in the groin.

Interferon: A protein produced by various cells in the body. Large quantities of different interferons may be produced in the laboratory. These proteins are used in the treatment of some forms of cancer. Interferon is a type of biological response modifier.

Interleukins: Proteins that carry regulatory signals between blood-forming cells. Large quantities of interleukins can be produced in the laboratory and used to treat some forms of cancer. Interleukins are biological response modifiers.

Intrathecal: Into the fluid around the brain and spinal cord—a way of injecting drugs.

Intravenous: Into a vein—a way of injecting drugs.

In vitro: In an artificial environment. Literally meaning "in glass". Used to describe studies carried out on living cells or tissues grown in the laboratory.

In vivo: In the living body. Used to describe a process or reaction occurring therein.

Ions: Atoms or groups of atoms that have an electrical charge.

Karyotype: The chromosome characteristics of an individual. Analysis can provide valuable information to aid in diagnosis and selection of treatment.

Leukapheresis: A blood filtering process used to remove extra lymphocytes.

Leukemia: Cancer that begins in developing cells in the bone marrow. Leukemia occurs when immature or mature cells multiply in an uncontrolled manner in the bone marrow. It is classified as lymphocytic or myeloid, according to the type of cell that is multiplying abnormally, and either acute, signifying rapidly progressing disease with a predominance of highly immature (blastic) cells, or chronic, which denotes slowly progressing disease with greater numbers of more mature cells.

Leukemogenesis: The cause, development, and progression of a leukemic disease.

Leukocytes: White blood cells.

Leukocytosis: An increase in the number of leukocytes in the blood.

Leukopenia: A below-normal number of white blood cells.

Lymph: The almost colourless fluid that bathes the body tissues and carries cells that help fight infection.

Lymph nodes: Small bean-shaped structures in the lymphatic system. The lymph nodes store special cells that can trap bacteria or cancer cells travelling through the body in lymph.

Lymphadenopathy: Disease of the lymph nodes.

Lymphatic system: The tissues and organs (including the bone marrow, spleen, thymus, and lymph nodes) that produce and store cells that fight infection and the network of vessels that carry lymph.

Lymphocytes: A type of white blood cell.

Lymphocytopenia: An abnormally low number of lymphocytes.

Lymphoid: The lymphatic system including lymphocytes and lymph nodes.

Lymphoma: Cancer of the lymphatic system, which is composed of the tissues and organs that produce and store cells that fight infection and disease. The lymphatic system includes the bone marrow, spleen, thymus, lymph nodes, and a network of vessels that carry fluid and infection-fighting cells. Lymphomas fall into two categories: Hodgkin's Disease and Non-Hodgkin's lymphomas.

Magnetic resonance imaging (MRI): A technique that uses an intense magnetic field to generate images of the internal organs. Properties of normal and cancerous tissue differ, and this allows malignant tumors to be visualized by computer processing of the signals detected.

Marrow fibrosis: The development of fibrous tissue in the bone marrow. Marrow fibrosis interferes with blood cell production.

Median age: In a list of ages arranged from youngest to oldest, the median age is in the center; half of the ages in the list are below the median and half are above it.

Medullary: In the central or inner portion; the medullary portion of the bone is the bone marrow.

Metabolism: A general term for the physical and chemical processes and reactions to them taking place in the body. These processes are primarily concerned with the way nutrients are used in the body.

Metastasis: The spread of cancer cells to other areas of the body through the lymphatic system or the bloodstream.

Mitosis: The usual process of cell reproduction that results in the formation of two daughter cells with exactly the same chromosome DNA content as that of the original cell.

Molecule: A group (aggregation) of atoms chemically combined to form a unique chemical substance.

Monoclonal antibodies: Antibodies specific for a single antigen. They can be produced in large quantities in the laboratory. Monoclonal antibodies are being studied in clinical trials to determine their effectiveness in cancer detection, diagnosis, and treatment.

Monocytes: One type of white blood cell. Monocytes (macrophages) play a key role in phagocytosis. They also interact with lymphocytes to regulate the immune response.

Mononuclear cells: Monocytes and lymphocytes; white blood cells other than granulocytes.

Monosomy: Possessing only one copy of a particular chromosome instead of the normal two copies.

Morbidity: A sick or diseased state.

Morbidity rate: The frequency of the appearance of complications following a surgical procedure or other treatment.

Morphology: The science of forms and structures of organisms; the form and structure of a particular organism, organ, or part.

Mucositis: Inflammation of the mouth and throat, which may be caused by anti-leukemia drugs.

Mutagenic: Causing a permanent change in genetic material (DNA).

Myeloablative: The conditioning regimen prior to transplant in which the bone marrow stem cells are destroyed or ablated. Generally, the conditioning regimen contains very high doses of chemotherapy and often includes total body irradiation.

Myelodysplastic syndromes: Conditions that result when blood cells fail to form or reproduce normally.

Myeloid: A collective term for the non-lymphocyte groups of white blood cells. It includes cells from the granulocyte, monocyte, and platelet lineages.

Myeloproliferative disorders: A group of relatively rare hematologic diseases characterized by abnormal excess growth of cells in the bone marrow. The myeloproliferative disorders include, polycythemia vera (PV), essential thrombocythemia (ET), agnogenic myeloid metaplasia (AMM), also referred to as idiopathic myelofibrosis (IMF), and chronic myelogenous leukemia (CML).

Myelosuppression: A condition in the bone marrow that results in fewer platelets, red blood cells and white blood cells.

Neoplasm: An abnormal growth (tumor) that starts from a single altered cell; a neoplasm may be benign or malignant. Cancer is a malignant neoplasm.

Neuropathy: Damage to the nerves that may occur as a complication of treatment for leukemia. It usually affects the nerves in the arms and legs and may be reversible when treatment is reduced or stopped.

Neutropenia: A below-normal number of neutrophils.

Neutrophils: A type of white blood cell (also known as a polymorphonuclear neutrophils or PMNs). Neutrophils are a type of granulocyte and are a primary defence against bacterial invasion.

Night sweats: Profuse sweating of the body during the night.

NK (natural killer) cells: Large lymphocytes that attack certain cells on contact and probably help regulate the immune system.

Non-Hodgkin's lymphoma: A cancer of the lymphatic system. What distinguishes non-Hodgkin's lymphoma from Hodgkin's lymphoma is the absence of a type of cell called

the Reed-Sternberg cell. This cell is present only in Hodgkin's lymphoma. The treatment methods for Hodgkin's and non-Hodgkin's lymphomas are very different.

Non-myeloablative: The conditioning regimen prior to transplant in which limited amounts of chemotherapy are administered in order to prevent rejection of the donor bone marrow stem cells without destroying the recipient's bone marrow.

Nuclear: Having to do with the nucleus of a cell. The nucleus is considered the control center of a cell.

Nuclei: Plural of nucleus.

Nucleus: The part of a cell that contains genetic information. The nucleus is considered the control center of the cell.

Oncogene: A type of gene that is normally inactive. When these genes are "turned on" (activated), they cause normal cells to change into cancer cells.

Oncogenic: Capable of causing cancer.

Oncologist: A doctor who specializes in studying and treating cancer.

Oncology: The study of cancer.

Opportunistic: An organism capable of causing disease only in a host whose resistance is lowered—usually by other diseases or by drugs.

Palliative care: Treatment that relieves symptoms, such as pain, but is not expected to cure the disease. The main purpose is to improve the patient's quality of life.

Pancytopenia: A condition in which there are reduced numbers of all types of blood cells.

Partial remission: The reduction, but not complete disappearance, of cancer in response to therapy.

Pathologist: A doctor who specializes in examining tissue and diagnosing disease.

-penia: A suffix which indicates abnormally low numbers of blood cells. Examples include, leukopenia, thrombocytopenia, and erythropenia.

Peptide: Two or more amino acids chemically bonded to form a single molecule.

Performance Status: A classification used for describing the status of cancer patients. The World Health Organization (WHO) defines performance status in terms of the following grade levels: 0 – able to carry out all normal activity without restriction; 1 – restricted in physically strenuous activity but ambulatory and able to do light work; 2 – ambulatory and capable of self-care but unable to carry out any work; 3 – capable of only limited self-care confined to bed or chair 50% or more of waking hours; and 4 – completely disabled and cannot carry on any self-care.

Peripheral blood: Blood circulating throughout the body.

Peripheral neuropathy: Numbness, tingling, burning, and weakness in the extremities. This condition usually affects the hands and feet and may occur as a complication of chemotherapy.

Petechiae: Tiny red spots under the skin; often a symptom of leukemia.

Phagocytosis: The process by which phagocytes (literally, cell eaters) surround and destroy micro-organisms or any foreign matter.

Pheresis: A procedure in which blood is removed from a donor, separated, and a portion retained, with the remainder being returned to the donor.

Philadelphia chromosome: An abnormal chromosome that is formed when part of chromosome 9 attaches to chromosome 22 (translocation). This abnormality is found in nearly all cases of chronic myeloid leukemia. Also called Ph1.

Plasma: The liquid portion of the blood.

Plasma cells: Large cells derived from the lymphocytes that form antibodies. Plasma cells are normally restricted to the bone marrow and lymph nodes and are not found in circulating blood.

Platelets: Blood cells that help to control bleeding by inducing clotting. Also called thrombocytes.

Pneumocystosis: Pneumonia resulting from infection with *Pneumocystis carinii*, frequently seen in immunologically compromised or steroid-treated individuals.

Polymerase chain reaction (PCR): A laboratory process in which a particular DNA segment from a mixture of DNA chains is rapidly replicated, producing a large, readily analyzed sample of a piece of DNA.

Postherpetic neuralgia (PHN): Pain that continues after the rash from shingles has healed.

Preleukemic condition: A disease of the blood that is not yet cancer but may become leukemia in the future.

Progenitor cell (also Precursor cell): An immature cell in the bone marrow which is responsible for producing mature blood cells.

Prognosis: The probable outcome or course of a disease; the chance of recovery.

Prolymphocytic leukemia (PLL): A variant of chronic lymphocytic leukemia in which the malignant cells have a more immature appearance.

Prophylaxis: An attempt to prevent disease.

Protein: A large number of amino acids chemically bonded in a chain. Proteins are large peptides.

Protocol: A schedule of treatment.

Purging: Removal of tumor cells from harvested bone marrow or blood before autologous transplantation.

Purpura: A condition characterized by the occurrence of purple spots on the skin, often accompanied by bleeding from the gums.

Radiation therapy: Treatment with high-energy rays to kill cancer cells. Also called radiotherapy.

Radiologist: A doctor who specializes in using radiation to diagnose or treat disease.

Receptor: A molecule on the cell surface or in the cytoplasm that fits another molecule like a lock and a key.

Refractory: Not responding favorably to treatment.

Relapse: The reappearance of signs and symptoms of disease after treatment.

Relative survival rate: A survival rate that takes normal life expectancy into account; the likelihood that a patient will not die of his or her disease by some specified time after diagnosis.

Remission: A period in which there is no evidence of disease on physical examination or examination of the bone marrow and blood.

Rescue process: The infusion of harvested bone marrow or peripheral blood stem cells into a patient who has undergone high-dose therapy.

Respiration: Breathing—the exchange of oxygen and carbon dioxide between the atmosphere and the body's cells.

Retrovirus: One of a large group of RNA viruses that are capable of copying and transferring genetic material.

Richter's syndrome: Transformation of CLL to diffuse large cell lymphoma.

RNA: Ribonucleic acid; nucleic acid is present in all living cells. RNA controls protein synthesis by transplanting the genetic information within the cell.

Secondary leukemia: Leukemia (most often AML) that arises when bone marrow is damaged by chemotherapy given to treat certain types of cancer or other diseases.

Shingles: A viral infection that may occur in a person who has previously had chicken pox. Shingles or zoster is the reactivation of the chicken pox virus (varicella).

Somatic mutation: The alteration of a gene in the cells of a specific tissue causes the gene to become a cancer-causing gene or oncogene. It is called “somatic” to distinguish it from germ cell mutation which, can be passed from parent to offspring. Most cases of leukemia are caused by a somatic mutation in a primitive marrow (blood-forming) cell.

Spleen: An organ on the left side of the abdomen near the stomach that plays an important role in immune system activities. It produces lymphocytes, filters the blood, stores blood cells, and destroys those that are aging. It is part of the lymphatic system.

Splenectomy: Surgical removal of the spleen.

Splenic lymphoma with villous lymphocytes (SLVL): A lymphoma similar to chronic lymphocytic leukemia. An enlarged spleen and abnormal cells with a single nucleus and irregular cytoplasmic projections are characteristic of SLVL.

Splenomegaly: Enlargement of the spleen.

Spinal tap: A procedure in which a needle is inserted into the space surrounding the spinal cord in order to withdraw cerebrospinal fluid. The cerebrospinal fluid is then analyzed in a laboratory for evidence of disease. Also called a lumbar puncture.

Stable disease: Blood work shows little variation over time. Stable disease for months or years is common among low-grade chronic leukemias. This condition is sometimes referred to as smoldering disease.

Stem cells: The immature cells from which all blood cells develop. These cells may divide to form more stem cells or mature into a variety of blood cell types.

Stomatitus: Inflammation of the mouth.

Syngeneic bone marrow transplantation: Grafting between two genetically identical individuals (identical twins).

Systemic: Affecting the body as a whole.

T-cells: (thymus derived cells) White blood cells that are important in the body’s immune system. Also know as T-lymphocytes, they mature in the thymus.

Thrombocytes: Platelets.

Thrombocytopenia: A below-normal number of platelets in the blood.

Thrombocytosis: A condition in which too many platelets are found in the blood.

Thymus: A small gland located in the top of the chest, behind the breastbone and between the lungs. The thymus plays a major part in the immune system.

Tinnitus: Noises in the ears including, ringing, whistling, booming, etc.

Total body irradiation (TBI): Radiation aimed at the entire body to destroy cancer cells. This procedure is often used in bone marrow transplants.

Translocation: Breakage and removal of a large segment of DNA from one chromosome, followed by the segment's attachment to a different chromosome.

Trisomy: The presence of an additional whole chromosome.

Tumor burden: The amount of cancer cells that are present in the body.

Tumor lysis syndrome: A side effect of chemotherapy that results from the rapid breakdown of leukemia cells. When leukemia cells are destroyed, they release breakdown products and minerals into the bloodstream, which may affect the kidneys, heart, and nervous system. This condition can be prevented by giving extra fluids and certain drugs, such as sodium bicarbonate, and allopurinol, which help the body dispose of these substances. Tumor lysis syndrome is more common with acute leukemia than with chronic leukemias.

Tumor suppressor gene: A protective gene that normally limits the growth of tumors. When a tumor suppressor is mutated, it may fail to keep a cancer from growing. BRCA1 and p53 are well-known tumor suppressor genes.

Ultrasound: Images of the body's internal organs that are created from the interpretation of reflected sound waves.

Uric acid: A waste product created when the body digests and uses food and liquids.

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer.