Leukemia simply means cancer of the white blood cells. They are usually diseases of unknown etiology, characterized by abnormal and uncontrolled proliferation of the leukocytes. What differentiate leukemias from other solid tumors is that the disease is widespread and involves most of the bone marrow right from the start of the disease, whilst such dissemination in other malignant disorders would have indicated an advanced disease stage. This bone marrow white cell proliferation may be associated with the appearance of immature leukocytes in the peripheral blood.

Leukemias are historically divided into acute and chronic, depending on whether the disease would last a short (weeks or months) or a long (perhaps years) period of time from the diagnosis, if left untreated. Over the last few decades, with the advent of new chemo-radiotherapeutic measures and through a better understanding of the behavior and biology of the different leukemic cells, this traditional concept has changed so much that acute no more means a bad disease and chronic does not necessarily indicate a better leukemia.

Currently more than two third of children with acute lymphoblastic leukemia (ALL), the commonest pediatric malignancy, can be cured of their disease. On the contrary, that cure rate can hardly be achieved in chronic leukemias. I think time is ripe to change this terminology so that acute no more means bad and chronic not necessarily good. Unfortunately, these terms are so deeply rooted into the mind of everybody that any such attempt will be counterproductive. What will be a real solution is to use the same terminology, but they should now be understood according to the new developments in the field, so that acute and chronic will have different connotations.

To understand the different varieties of leukemias according to the new concepts, one should have a clear idea about the process of hemopoiesis. As it is evident from the figure in the next page, bone marrow stem cells will produce mature cells through many steps of self-renewal and progressive differentiation and maturation. Immature, early or primitive blast cells will finally produce mature peripheral blood cells. Acute leukemias can now be thought of as malignancy of the primitive cells, and chronic leukemias as malignancy of the mature and maturing cells. Indeed it is now possible to draw a line between cells whose proliferation cause acute leukemias and cells whose proliferation cause chronic leukemias. Grasping this fact means that from now on it will be better to think of acute leukemias as blast cell leukemias, whose proliferating cells are above our imaginary line, and chronic leukemias as mature cell leukemias involving proliferation of cells below the line. In this way we will have the best of the old and new classifications.
MYELOID/LYMPHOID STEM CELLS

LYMPHOID S/C

Pre-T  Pre-B  Pro-normoblast  Pro-myelocyte
Thymocyte

MYELOID S/C

Pro-normoblast  Myeloblast  Mega-karyoblast

Pre-T

Pre-B

CHRONIC LEUKAEMIAS

T-Cells

B-mature

LPC

"T" Helper

"T" Supp.

Plasma cell

Red cell

HPC

"T" Helper

"T" Supp.

Plasma cell

HPC

Helper

Supp.

B-virgin

Myelocyte

Metamyelocyte

Stab Cell

Platelet

HEMATOPOIESIS WITH A LINE DEMARCATING ACUTE FROM CHRONIC LEUKAEMIAS

INCIDENCE OF LEUKAEMIAS:

To have an idea about leukemias in Kurdistan, you have to visit Nanakalee hospital in Hawler or Hewa hospital in Sulaimania! Leukemias constituted around 10% of the malignant cases admitted to the Asir central hospital of Saudi Arabia, where I practiced hematology for almost two decades. In the developed world, like the United States, where cancer registry is available, leukemias represent only 3 percent of the total number of cancer patients. However, this is a real underestimation in the term of utilization of resources, if one compares this curable disease with other cancers in which survival is measured in months, if not weeks. A child with acute lymphoblastic leukemia might stay under treatment for years, while a hepatoma, lung cancer or a brain tumor patient hardly stays alive for more than few months.
TYPES OF LEUKEMIAS:

As mentioned, leukemias are either acute or chronic. Each type can be lymphoid or myeloid. So there are four main varieties of leukemias:

1. **Acute Lymphoblastic Leukemia (ALL).**
   - This is the commonest malignancy of children (80% of acute leukemias in children).
   - **CHILDREN**

2. **Acute Myeloid Leukemia (AML).**
   - (80% of young adult's acute leukemias).
   - **STUDENT'S AGE**
   - (In the West, mainly **ELDERLY**)

3. **Chronic Myeloid Leukemia (CML).**
   - Usually affects middle-aged people.
   - **FATHER'S AGE**

4. **Chronic Lymphocytic Leukemia (CLL).**
   - This is the leukemia of the elderly people.
   - **GRAND-FATHER'S AGE**
   - **ALL** is 20%, **AML** is 25%, **CML** is 30% and **CLL** is 25% of all the leukemias.

ACUTE LEUKEMIAS

Clinical Features:

Leukemias are usually easy to diagnose but difficult to manage. Proper management aiming at curing patients needs patience, compliance, resources and time.

It is quite easy to imagine how a patient with acute leukemia presents himself. Bone marrow produces red cells, white cells and platelets. Leukemia, by infiltrating the bone marrow, causes reduction of these cellular elements. As a result the patients will present with anemia, neutropenia and thrombocytopenia. To translate these to clinical terms, there will be pallor, tiredness, easy fatigability from the anemia; infection from the neutropenia and bleeding from thrombocytopenia. Organs infiltration by leukemia could cause lymph node enlargement, splenomegaly, testicular swelling or meningeal irritation. Monoblastic leukemias have tendency to infiltrate the gum, skin and lymph nodes. Many of our children with acute leukemia present with bone pain and joint manifestations for which they have been seen for weeks by the pediatrician on the suspicion of having rheumatic fever or juvenile rheumatoid arthritis.

Infections are usually bacterial in the early stages. After prolonged periods of neutropenia fungal infections become a real problem especially after multiple courses of chemotherapy and antibiotics. Viral infections like herpes simplex should be taken quite seriously in the immunocompromized leukemic patients. Measles and chicken pox are problematic in children on prolonged treatment.

Thrombocytopenia causes bleeding. Bleeding into the skin and mucus membrane is called purpura. If these bleeding points are tiny they are called petichae. Larger ones are called purpura. Bruise is a large bleeding spot on the skin. Diffuse superficial skin bleeding is termed ecchymosis. A large collection of blood subcutaneously is called hematoma. Frank vaginal or GI bleeding could be the presenting feature in leukemia patients.

There was a lot of confusion regarding the proper naming of the different types of leukemias. That was not a real problem during the era when no treatment was available and the disease was universally fatal. The French-American-British (FAB) and currently W.H.O. classification have surfaced up to solve this problem and to create some uniform understanding between different countries.
FAB  
(FRENCH AMERICAN BRITISH)  
CLASSIFICATION OF ACUTE LEUKEMIAS

Acute Lymphoblastic Leukemias (ALL):

Acute Lymphoblastic Leukemias (L1): Small, monomorphic lymphoblasts.  
Nuclei are round and regular. Nucleoli not visible. 
Cytoplasm is scanty.

Acute Lymphoblastic Leukemias (L2): Large and heterogeneous lymphoblasts.  
Irregular nuclear outline. Nucleoli prominent.  
Usually abundant amount of cytoplasm.

Acute Lymphoblastic Leukemias (L3): Large very uniform in size and shape.  
Deeply basophilic and vacuolated cytoplasm.  
As a fast growing tumor, mitotic figures are seen

Acute Myeloid Leukemias (AML):

M0 Acute Undifferentiated Myeloid Leukemia
M1 Acute Myeloid Leukemia without maturation
M2 Acute Myeloid Leukemia with maturation
M3 Acute Hypergranular Promyelocytic Leukemia
M4 Acute Myelomonocytic Leukemias
M5 Acute Monoblastic Leukemias
M6 Erythroleukemia
M7 Acute Megakaryoblastic Leukemia

M1= Myeloblasts  M2= Myeloblasts + Promyelocytes  
M3= Promyelocytes  M4= Myeloblasts + Monoblasts  
M5= Monoblasts  M6= Myeloblasts + Pronormoblasts  
M7= Megakaryoblasts

Currently, W.H.O. has pioneered and published a new classification in their blue books  
that is becoming the standard classification for all leukemias. Cytogenetic changes and  
immunophenotyping have a great impact on this new W.H.O. classification.

Diagnosis depends on examining properly stained blood smears and bone marrow  
aspirations. In acute leukemias, the white cells could be low, normal or high depending on  
whether the leukemic cells in the bone marrow infiltrate the blood or not. The bone marrow  
should always have excessive numbers of blast cells. One cannot make the diagnosis of acute  
leukemias without more than 30% (now even 20%) blast cells in the marrow. Normally blast  
cells are <2% of the bone marrow. In chronic leukemias, the white cell count is always high.

Usually it is possible to make the diagnosis by looking at the morphology of the leukemic  
cells. To differentiate ALL from AML and for the identification of the exact FAB group, one  
might need SPECIAL STAINS and IMMUNOLOGICAL MARKERS. Chromosomal changes  
associated with certain subtypes of acute leukemias could add much to our knowledge.
Difficulties arise in differentiating between L2, M1 and M5 because the type of the blast cells could be difficult to recognize. The usual special stains used are:

- **PAS** “Periodic Acid Schiff” which is usually positive in Lymphoblasts
- **Myeloperoxidase (MPO)** & **Sudan Black (SB)** are positive in Myeloblasts
- **Double Esterase** is composed of Specific and Non-Specific Esterases:
  - Specific Esterase is “**Chloroesterase Esterase**” which resembles MPO and SB in Myeloblasts
  - Non-Specific Esterase is “**Butyrate Esterase**” is positive in Monoblasts

**Immunological markers:**

This has revolutionized the arena of acute leukemia diagnosis especially ALL. You are welcome to go through the nine-page review article I wrote for the Saudi Medical Journal about this important topic. Much of our progress in the management of acute leukemias has come about through these advances in the diagnosis of specific types of leukemias and tailoring our treatment to the particular type of the disorder. Immunological markers are present on the surface, in the cytoplasm and in the nuclei of the leukemic cells. The surface markers are by far the most abundant and now can be detected by monoclonal antibodies produced against them. There are hundreds of cell surface markers, which are now designated by “CD”s or Cluster Designations. By running the leukemic cells through the Flow Cytometer machine and labeling them with these monoclonal antibodies that are attached to fluorochromes, we can detect precisely the specific CDs and reach the exact diagnosis of the type of leukemia. This is one of the miracles of medicine that has helped us to diagnose different types of leukemias with confidence and without too much reliance on subjective parameters like interpretation of marrow and blood smears.

Acute Leukemias are due to immunological arrest in the maturation and differentiation of the cell production. This arrest leads to accumulation and increase in the number of the leukemic cells. By immunologically examining these cells, we can reach the precise diagnosis of the type of the leukemia.

A very useful nuclear marker is **TdT** (don't worry about the detailed name of this enzyme but it is Terminal deoxynucleotidyl Transferase), which differentiates ALL from AML. TdT is usually positive in ALL.

The commonest children's leukemia is positive for a marker called common ALL antigen **CALLA**. CALLA is equivalent to **CD10**. Cells positive for this antigen is said to be a common precursor for B and T lymphocytes. In **Pro-B ALL**, TdT, HLA-DR & CD10 are positive. ALL due to proliferation of cells beyond the stage of common ALL is called **Pre-B ALL**; these cells are also positive for a new cytoplasmic marker called Cytoplasmic μ. Clinically this type of ALL behaves like Pro-B ALL with a mild clinical course and a good response to treatment. **T-ALL** is positive for T-Cell markers. CD7 is the most useful marker. Other T-Cell markers are **CD2**, and **CD5**. T-ALL is known to be associated with high white cell count and mediastinal involvement. Before the advent of intensive treatment, prognosis used to be poor but now this view is untrue.

The last, worst and rarest (<1%) type of ALL is called **B-ALL**. It is positive for SmIg but negative for TdT. It is equivalent to Burkitt's leukemia or L3 of the FAB morphological classification.
Immunophenotyping has also found its role in the diagnosis of AML. CD33 and CD13 are very useful markers and are usually positive in the majority of patients with AML. CD14 is positive in Monoblastic AMLs and CD41 & CD42 and CD61 in M7. TdT is usually negative.

<table>
<thead>
<tr>
<th>ALL</th>
<th>TdT</th>
<th>HLA-DR</th>
<th>CD10</th>
<th>Cyt. µ</th>
<th>Smlg</th>
<th>CD19-22 (B-Lineage)</th>
<th>CD 2-8 (T-Lineage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-B</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pre-B</td>
<td>+</td>
<td>+</td>
<td>++</td>
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</tr>
<tr>
<td>B-ALL</td>
<td>-</td>
<td></td>
<td></td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-ALL</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Management of Acute Leukemia:
Kindly see the protocol for the detailed month by month management of acute lymphoblastic leukemias. AML is treated with induction courses of Daunorubicin and Ara-C and consolidated with high dose Ara-C. ALL treatment takes years and better be understood as per the protocol.
Like acute leukemias, chronic leukemias are also caused by abnormal, uncontrolled and widespread proliferation of white blood cells, but the difference is that instead of marrow infiltration by blast cells, here there is proliferation of mature and maturing white cells. In acute leukemias, the marrow is full of blast cells (must be more than 20%) and these primitive harmful cells reside in the marrow and can also come out to the peripheral blood. That means in acute leukemias white blood cells can be normal, low or high. In chronic leukemias, the mature white cells have tendency to permeate the peripheral blood and the white cell count is always high.

There are two types of chronic leukemias, depending on whether it is the myeloid line or the lymphoid line that is proliferating. Chronic Myeloid Leukemia (CML) results from proliferation of the mature and maturing Granulocytes while Chronic Lymphocytic Leukemia (CLL) results from increased numbers of mature lymphocytes.

(CML)

Chronic Myeloid Leukemia

This is a clonal disorder that results from a stem cell abnormality. This alteration in the stem cell leads to marked proliferation of mature and maturing granulocytes. It is now known that the diagnostic Philadelphia (Ph) chromosome, that is positive in the majority of these patients, has something to do with this malignancy. Translocation between the long arms of chromosomes 9 and 22 \([ t(9;22) ]\) creates an oncogene that codes for a protein called Tyrosine Kinase that leads to persistent proliferation of the white cells.

The hallmark of the disease is leukocytosis, splenomegaly and positive Ph chromosome. Because of the markedly short half-life of the neutrophils (hours only) and the tremendous expansion of the granulocyte mass, many of these patients show feature of hypermetabolism like sweating, weight loss, hyperuricemia and may be gout. Hyperleukocytosis can cause painful erection of the penis (priapism) and cerebral leukostasis.

Spleen can reach a great size and might fill the abdomen. CML is a common cause of marked splenomegaly. Big spleen can press the stomach causing reduction in the amount of food that the patient can eat. It can press the bladder, causing increased frequency of micturition. Patients with marked splenomegaly are under continuous dragging pressure and pain from their big spleen and might even have repeated acute abdominal pain from infarctions of the big spleen.

Despite all of these possible clinical features, nowadays we are diagnosing many of these patients incidentally, when they are doing blood tests for other reasons. That means at least in early stages, majority of these patients are asymptomatic.

CML usually affects middle-aged people at around 50 years of age. It was one of the commonest leukemias where I practiced in Saudi Arabia. I had more than a hundred patients at any one time. Over the last three years in Kurdistan, I have been seeing an average of a case a month in each of Hawler and Sulaimania and a referral from the other Kurdish cities. The annual incidence is said to be 10 per million.
The median survival of CML patients in the west is around 3 to 4 years. This has not been our experience in the Middle East. We usually expect twice as long survival in our patients. Now with the new treatment Imatinib “Glivec”, survival could be counted in decades rather than years.

What is very interesting about CML is the predictability of the disease. Although God alone can foresee with certainty what happens to his subjects, he has empowered us with knowledge to predict what happens to our patients. Nowhere in medicine this is more true than CML. When we diagnose a fresh patient with CML, we know that the disease can go on for years (usually 3 to 4 or even more) in a chronic phase of the disease and then the disease gets out of control in two ways. Either the CML will transform into an acute leukemia and the patient dies in the matter of few months “**Blast Crisis**” or there will be a more gradual worsening of the condition in what is called “**Accelerated Phase**”. After around six months in the Accelerated Phase (again in my experience, this can go on for two years) the disease yet again terminates in Blast Crisis with a very poor outcome.

**CHRONIC PHASE** \[\rightarrow\]** ACCELERATED PHASE** \[\rightarrow\]** BLAST CRISIS**

So CML is a biphasic or usually a triphasic disease. During the Chronic Phase of the disease, the progression of the disease is very slow. Patients can expect a comfortable four or more years of survival during which their disease responds very well to treatment and their WBC and splenomegaly can be put under control. The white cell count can reach hundreds of thousands but their morphology is usually normal and generally speaking patients don’t have infectious problems. It is usually the mature neutrophils and myelocytes that are increased. Going back to the myelopoiesis, we can imagine better what is the situation:

<table>
<thead>
<tr>
<th>Myeloblast</th>
<th>Promyelocyte</th>
<th>Myelocyte</th>
<th>Metamyelocyte</th>
<th>Band</th>
<th>Neutrophil</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>(+)</td>
<td>(+)</td>
<td>(++)</td>
<td>(++++)</td>
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</tr>
</tbody>
</table>

As you notice, it is basically the mature neutrophils and myelocytes that are increasing. **Blast** cells are less than 5% in the chronic phase of the disease; more than 20% in the Blast crisis and between 5 and 20% in the Accelerated Phase.

CML must be differentiated from **Leukemoid reaction**, a benign conditions that is usually secondary to infections, intoxications and other malignancies. In Leukemoid reaction the white cells are usually under 100,000/uL, the Ph chromosome is negative and the score of Neutrophil Alkaline Phosphatase (NAP) is increased. The types of cells are also different. While in CML, it is basically neutrophils and myelocytes that are increasing, with a leukemic hiatus in between; in Leukemoid reaction the final stages of granulopoiesis are increased in order.

<table>
<thead>
<tr>
<th>Myeloblast</th>
<th>Promyelocyte</th>
<th>Myelocyte</th>
<th>Metamyelocyte</th>
<th>Band</th>
<th>Neutrophil</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>(++)</td>
<td>(++)</td>
<td>(++++)</td>
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</tbody>
</table>

**NAP** is a diagnostic test in CML because it is markedly decreased. White cells are stained for Alkaline Phosphatase and a hundred of them will be scored; each is given anything from zero (when not stained at all) to 4 (when it is very densely stained). That means the total score could be anything between zero to 400. Normal NAP score is between 35 & 100. In CML, it is almost undetectable with the score approaching zero. In leukemoid reaction, it is usually more than a hundred.
As mentioned, the disease is quite predictable during the chronic phase. After many years of good control, the patient becomes less responsive to chemotherapy. The splenomegaly and leukocytosis need higher doses of medication to be put under control. The blast cells increases and basophils and eosinophils become quite prominent. Platelet count can reach a million per uL or even higher. Anemia worsens and there might be more marrow fibrosis. These features and new chromosomal changes indicate transformation of the disease to the Accelerated Phase. So far the blast cells are below the 20% mark. Once the blast cells exceeds 20% then the patient is in the Blast Crisis. Patients in Blast Crisis can have fever, lymphadenopathy and rapidly worsening clinical course.

Although platelet count is on the high side in CML, their function is usually defective. Bruises and bleeding from GIT and GUT is quite a problem in CML patients especially when the patient enters the more advanced stages.

**Other types of CML:**

The typical scenario mentioned above of a CML patient going predictably through the aforementioned stages is the normal sequence of events in more than 90% of cases. Quite a minority have atypical features with more abnormal looking blood cells, lack of Ph chromosome, etc. This “Atypical CML” have poorer prognosis and is less responsive to treatment.

In CML, Monocyte ratio is low. When there is Monocytosis in CML, the condition is called Chronic Myelomonocytic leukemia “CMML”. This is yet another type of CML.

Occasionally the CML involves the eosinophils or the basophils, instead of neutrophils. These are called “*Chronic Eosinophilic*” and “*Chronic Basophilic*” Leukemias.

There is also a rare type of CML in Children called “*Juvenile CML*”. These patients are not positive for Ph chromosome, usually present with facial rash and lymphadenopathy.

**Management of CML:**

*Busulphan* (Myleran) used to be the cornerstone in the management of CML for decades. This drug had not changed the course of the disease and did not prolong the life of these patients. It could control the WBC count and shrink the spleen size, but its impact on the evolution of the disease to more advanced stages was minimal or nil. It was marrow suppressive and many patients suffered prolonged periods of pancytopenia. Busulphan could also cause skin pigmentation, pulmonary fibrosis and other complications.

The next line of management came with *Hydroxyurea*. A potent CML drug with less side effects and a much shorter duration of action, giving us more freedom over its use. Again impact of this superb drug over the survival of CML patients has not been much.

When we diagnose a patient with CML, we know that despite many years of comfortable life, this patient is going to die from his disease with the conventional management. When the patient is young, one wishes for a more drastic measure that can save the life of the patient and cure him. Thank God this is now possible with Stem Cell or Bone Marrow Transplantation. This can cure more than two thirds of these patients and should be offered to any patient who can have the operation and has a histocompatible donor. Nowadays *Glivec “Imatinib Mesylate”* is becoming the main modality of treatment that has extended life expectancy from years to decades and possibly has cured many patients.
CLL

Chronic Lymphocytic Leukemias

This is by far the commonest elderly leukemia. It is extremely rare in children and even in young adults. It is more common in males. It is the commonest leukemia in the west.

CLL results from progressive accumulation of lymphocytes. Unlike lymphomas, in which the lymphoid cell proliferation starts in the lymph nodes, CLL starts in the bone marrow, infiltrates the blood and then goes to the lymph nodes, spleen and other hemopoietic and lymphatic tissues. Actually, this slow progression is the basis for Rai’s staging for CLL, which will be discussed next.

The normal lymphocyte count is 1,500 to 4,000/μL and up to 20% of the bone marrow is composed of lymphocytes. In CLL, the marrow lymphocytes gradually build up and the lymphocyte count in the peripheral blood rises. When the marrow lymphocyte is more than 40% and the lymphocyte count is more than 15,000/μL, then we call it Stage “0”. After that, lymphocyte count increases in both the marrow and the blood and finally find their way to the lymph nodes. When there is lymphadenopathy, the CLL stage is “I”. With more proliferation of the lymphocytes, spleen and liver will also be involved. Splenomegaly or hepatomegaly denotes Stage “II”. With more proliferation of the lymphocytes, the bone marrow fails because it will be nearly totally replaced by the leukemia. This marrow failure causes anemia &/or thrombocytopenia. In Stage III, there is anemia and in Stage “IV”, there is thrombocytopenia.

This Rai staging is important because it gives us some idea about the survival of these patients. The last row of the following table illustrates that.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>FEATURES</th>
<th>SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Lymphocyte count: 1500-4000/μL</td>
<td>“GOK” God Only Knows</td>
</tr>
<tr>
<td></td>
<td>Marrow Lymphocyte: &lt;20%</td>
<td></td>
</tr>
<tr>
<td>“0”</td>
<td>Lymphocytosis &gt;15000/μL</td>
<td>150 months; Not much different from normal for CLL age.</td>
</tr>
<tr>
<td></td>
<td>Marrow Lymphocyte &gt; 40%</td>
<td></td>
</tr>
<tr>
<td>“I”</td>
<td>Above plus Lymphadenopathy</td>
<td>101 months</td>
</tr>
<tr>
<td>“II”</td>
<td>Splenomegaly or Hepatomegaly or both</td>
<td>71 months</td>
</tr>
<tr>
<td>“III”</td>
<td>Anemia (Hb &lt;11 gm/dL)</td>
<td>19 months</td>
</tr>
<tr>
<td>“IV”</td>
<td>Thrombocytopenia (Platelet &lt;100,000/μL)</td>
<td>19 months</td>
</tr>
</tbody>
</table>

RAI STAGING FOR CLL

Another staging system was proposed by Binet. In Binet staging, which was adopted by the International Workshop on CLL, there are three stages A, B & C. In the poor prognosis group “C”, there is bone marrow failure with anemia and thrombocytopenia. The remaining groups depend on the number of lymphoid organs involved. There are five lymphoid areas for that purpose: Neck, Axillae, Inguinal nodes; spleen and liver. In the good prognosis group “A”, there is either no lymph node enlargement, or up two areas. In the intermediate group “B”, there must be three to five regions involved. Rai did not include the number of lymph node regions involved!
STAGE FEATURES

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>“A”</td>
<td>Hb &gt; 10 gm/dL; Platelet &gt; 100 000/uL; No lymphadenopathy or less than two lymph node regions involved</td>
</tr>
<tr>
<td>“B”</td>
<td>Above plus three or more lymph node regions involved</td>
</tr>
<tr>
<td>“C”</td>
<td>Anemia &amp; /or Thrombocytopenia</td>
</tr>
</tbody>
</table>

INTERNATIONAL BINET STAGING FOR CLL

The lymphocytes in CLL are small, morphologically mature-looking with dense nuclear chromatin and very little amount of cytoplasm. These cells are so fragile, they might rupture during spreading of the film producing the diagnostic smear or smudge cells. Prolymphocytes could be seen but they should be less than 10%, otherwise the disease is called CLL/PLL.

Immunophenotyping is becoming very important in the diagnosis of lymphoproliferative disorders. CLL and SLL “Small Lymphocytic Lymphoma”, the tissue counterpart of CLL, are grouped together in the new W.H.O. classification. B cell markers “CD19, CD20, CD21 and CD22” are positive in CLL. CD5 and CD23 are also positive. Surface membrane Immunoglobulin is dim.

In Prolymphocytic Leukemia (PLL), the prolymphocytes predominate. These are larger cells with more cytoplasm and centrally located vesicular nucleoli. PLL usually affects more elderly people and the disease is much more progressive with very high lymphocyte count and marked splenomegaly. Lymphadenopathy is not a significant feature of PLL. Response to treatment is poor. In contrast to CLL cells, which are weakly positive for SmIg, PLL cells are immunologically more mature and thus strongly positive.

Hairy Cell Leukemia (HCL) is quite rare in Saudi Arabia and the Middle East. Over the last twenty five years of my practice in the Middle East, I have only diagnosed few patients. It usually affects middle-aged men who present with pancytopenia, monocytopenia and splenomegaly. Lymphadenopathy is not a usual feature. Bone marrow is difficult to aspirate (dry tap) but biopsy is diagnostic. The hairy cells in the blood are characteristic with hairy cytoplasmic projections. Hairy cells are positive for TRAP (Tartarate Resistant Acid Phosphatase) and CD11c, CD25 & CD103.

Anemia in CLL is usually due to bone marrow failure from leukemia infiltration. These abnormal lymphocytes might form antibodies against the red cells producing warm autoimmune hemolytic anemia (AIHA). The blood smear in this situation shows spherocytes and the marrow shows red cell hyperplasia. Coomb’s test is positive. Splenomegaly might cause hypersplenism, thus contributing to the anemia. Because CLL is a lymphoproliferative disorder, folic acid might be deficient, contributing to the anemia. These elderly people might also have nutritional deficiency, which also cause anemia.
**Management of CLL**

One should always remember the Hippocrate’s oath of “at least do no harm”. There is no cure in CLL, so the aim should be to prolong survival with good quality of life. Majority of these elderly patients die from other causes like cardiovascular or cerebral events and the CLL might be their least significant problem. This is particularly true for early stages of the disease in which survival is measured in tens of years. To treat a patient unnecessarily is to subject him to chemotherapy with all its side effects. The wisdom of watchful waiting (www) is particularly true for Binet’s stage A and Rai’s stage 0, I or even II.

Currently many tests are available that can guide us regarding the prognosis in CLL. A patient with Immunoglobulin gene mutation can expect prolonged survival. Zap70 and CD 38 positivity usually indicate poor prognosis and shorter survival.

Advanced stages of CLL with evidence of marrow failure and patients with positive Zap70/CD38 markers need prompt management. Steroid alone is lympholytic and might clear the marrow from lots of the leukemic cells without suppressing the marrow and exacerbating anemia, neutropenia or thrombocytopenia. It could be tried for a month before Chlorambucil is added. Chlorambucil has been the gold treatment for CLL. It could be combined with steroid or better be given alone. It is given on daily basis (2-6 mg) or as monthly pulse therapy. Cyclophosphamide is as effective as Chlorambucil. Many hematologists use COP chemotherapy as the primary form of therapy.

Recently Fludarabine has been found to be very effective, especially for Chlorambucil unresponsive patients. It is given intravenously at a dose of 25 mg/m$^2$ for five days each month. Unfortunately it can cause neutropenia and lymphopenia. It is advisable to give Septrin along with it.

Rituximab, a monoclonal antibody against CD20, has emerged as an effective agent in CLL, especially if it is combined with Fludarabine and Cyclophosphamide “FCR”.

Alemtuzumab “anti CD52” is used for relapsed and refractory patients.

Patients with CLL are immunocompromized with a high incidence of herpes simplex, zoster and other viral and fungal infections. Liberal use of antibiotics, antiviral and intravenous immunoglobulins are advisable.

Cladribine is an effective one time treatment for hairy cell leukemia.

Good Luck.

The presentation for this lecture can be found on [lectures.shanyar.com](http://lectures.shanyar.com)