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LEUKEMIA – BRIEF REVIEW ON RECENT ADVANCEMENTS IN THERAPY AND MANAGEMENT

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ABSTRACT
Leukemia is an amalgam of cancers and arises due to the malignancy of the any elements of blood and bone marrow. In other terms, they are abnormal white blood cells, which are not fully developed and are called blasts or leukemia cells. The growth of the Leukemia cells are rapid than Normal cells. As with time, they replace the population of the normal WBCs and RBCs and may spread to the lymph nodes and other organs. As in 2012, 3,52,000 People were affected by Leukemia and 2,65,000 Deaths occurred. It is the most common type of cancer in children and three quarters of Cases being) about 90% of all leukemias are diagnosed in adults, with acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) being most common in adults.

KEYWORDS
Leukemia, Lymphoblastic, Malignancy and Cancer.

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INTRODUCTION

Acute lymphocytic leukemia (ALL), also called acute lymphoblastic leukemia, is a cancer that starts from the early version of white blood cells called lymphocytes in the bone marrow (the soft inner part of the bones, where new blood cells are made).
Leukemia cells usually invade the blood fairly quickly. They can then spread to other parts of the body, including the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles (in males). Other types of cancer also can start in these

organs and then spread to the bone marrow, but these cancers are not leukemia.

The term “acute” means that the leukemia can progress quickly, and if not treated, would probably be fatal within a few months. Lymphocytic means it develops from early (immature) forms of lymphocytes, a type of white blood cell. This is different from acute myeloid leukemia (AML), which develops in other blood cell types found in the bone marrow. For more information on AML, see our document Leukemia-Acute Myeloid.

Other types of cancer that start in lymphocytes are known as lymphomas (non-Hodgkin lymphoma or Hodgkin disease). The main difference between these types of cancers is that leukemia’s like ALL mainly affects the bone marrow and the blood, and may spread to other places, while lymphomas mainly affect the lymph nodes or other organs but may involve the bone marrow. Sometimes cancerous lymphocytes are found in both the bone marrow and lymph nodes when the cancer is first diagnosed, which can make it hard to tell if the cancer is leukemia or lymphoma. If more than 25% of the bone marrow is replaced by cancerous lymphocytes, the disease is usually considered leukemia. The size of lymph nodes is also important. The bigger they are, the more likely the disease will be considered a lymphoma. For more information on lymphomas, see our documents Non-Hodgkin Lymphoma and Hodgkin Disease[1].

Causes of Leukemia[2]

The root casues of different types of Leukemia are unknown. There are many root causes and risk factors for any individual to develop Leukemia and proliferate into a fatal disease stage. The root causes are as follows:

- Prior chemotherapy
- Inherited syndromes
- Ionizing radiation
- Smoking and alcohol consumption
- Work involving chemicals
- Human T-cell leukemia virus-I (HTLV-I)
- Myelodysplastic syndrome
- Family History, Age.

Prior Chemotherapy

A subset of acute myeloid leukemia (AML), known as "secondary AML" or "therapy related myeloid leukemia," develops following treatment with chemotherapy. Although implied by the name, the exact mechanism remains unknown. Prognosis for secondary AML is generally unfavorable compared to primary AML.

Inherited Syndromes

There is a 20 % chance of developing Leukemia in children patients who have Down’s syndrome. The 10 % chances are for Transient Leukenia that resolves within months of birth. Other inherited syndromes that increase risk of leukemia include:

- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi syndrome
- Klinefelter syndrome
- Neurofibromatosis.

Ionizing Radiation

People exposed to high levels of radiation, mostly people who are survivers of Atomic explosion and Nuclear Plant accidents are known to develop Leukemia. Exposure to lower levels of radiation during radiotheraphy and X - rays also may be the risk[3].

Human T-cell leukemia virus-I (HTLV-I)

T-cell Leukemia/Lymphoma (ATLL), a cancer of activated mature T lymphocytes. Is directly linked to the Human T-cell leukemia virus-I (HTLV-I). HTLV-I and ATLL are widespread in certainregions of the world, such as the Caribbean basin, Japan, and parts of South America and Africa, while very rare in others. Most people who are infected with HTLV-I do not develop leukemia.

Smoking and alcohol consumption

Alcohol and smoking may induce toxic chemicals upon the liver and mutate the cells into Leukemia Cells. Smoking mostly leads to Acute Myelogenous Leukemia (AML).

Myelodysplastic syndrome

People with the blood disease are at increased risk of developing acute Leukemia, mostly of Myeloid type.

Age

Leukemia risk increases steadily with age. The curve for acutelympho blastic leukemia (ALL) incidence, however, is U-shaped: highest between the ages of 3-7

and rising again after the age of 40. The reason for this peak in early childhood.

Family history of leukemia

It's rare for more than one person in a family to have leukemia. When it does happen, it's most likely to involve chronic lymphocytic leukemia. Only a few people with chronic lymphocytic leukemia have a father, mother, brother, sister, or child who also has the disease.

TYPES OF LEUKEMIA

Physiologically and on the verge of occurance,
Leukamia is classified into different Types:
Based on Characteristics of the disease:

- Acute Leukemia
- Chronic Leukemia

Based on the types of WBCs affected:

- Lymphocytic Leukemia
- Myelogenous Leukemia

Acute Leukemia

Occurs due to the malignant transformation of Hemopoetic stem cells into undifferentiated primitive cell with abnormal longivity[4].

These lymphoid cells Acute Lymphocytic Leukemia [ALL] or myeloid cells Acute Myelogenous Leukemia [AML]-proliferate, replacing normal bone - marrow tissue and hematopoietic cells and inducing anemia, thrombocytopenia, and granulocytopenia. They can infiltrate various organs and sites, including the liver, spleen, lymph nodes, CNS, kidneys, and gonads as they are blood bourne.

Chronic Leukemia

A group of malignancies involving the hematopoietic system. Chronic myelogenous leukemia (CML) is a proliferation of myeloid neoplasm that arises from a clonal process involving an early progenitor hematopoietic stem cell. It also is associated with the *BCR-ABL1* fusion gene localized to the Philadelphia (Ph) chromosome[5,6].

Chronic myelomonocytic leukemia (CMML)

By World Health Organization (WHO) has been redefined as a myelodysplastic/myeloproliferative neoplasm. It originates from a clonal hematopoietic malignancy, in which there

Chronic lymphocytic leukemia (CLL)[7,8]

It is a neoplasm comprised of small, round to slightly irregular B lymphocytes.

ACUTE LYMPHOCYTIC LEUKEMIA

Basic Symptoms

- Feeling tired, weak or lightheaded
- Shortness of breath
- Fever
- Infections that don't go away or keep coming back
- Bruising easily
- Bleeding, such as frequent or severe nosebleeds and bleeding gums.

General symptoms

Patients with ALL also often have several non-specific symptoms. These can include:

- Weight loss
- Fever
- Night sweats
- Fatigue
- Loss of appetite.

Specific Symptoms[10]

- Swelling in the abdomen
- Enlarged lymph nodes in the sides of the neck, in the groin, under arm pits and in chest and abdomen
- Enlarged Thymus
- Bone and joint pain.

DIAGNOSTICS

Complete blood count (CBC) and blood cell exam (peripheral blood smear)

Too many immature white cells in their blood, Many of the white blood cells will be lymphoblasts (blasts), which are immature lymphocytes not normally found in the bloodstream. Lymphoblasts do not function like normal, mature white blood cells[9].

Bone marrow aspiration

More immature Lymphoblasts in bone marrow.

Chromosomal testing

A piece of chromosome is missing – deletion. Also 2 chrosomes attach as DNA swaps – Translocation[9]

Chromosomes might be short – Philadelphia chrosome with 22 chrosomes.

ADVANCES IN TREATMENT OF ALL

Treatment for Untreated Adult Acute Lymphocytic Leukemia

Remission induction therapy with supportive Care

Combination chemotherapy, Imatinib mesylate (for patients with Philadelphia chromosome [Ph1]-positive ALL), Imatinib mesylate with combination chemotherapy (for patients with Ph1-positive ALL:

CNS prophylaxis therapy

Cranial radiation therapy with intrathecal (IT) methotrexate, High-dose systemic methotrexate and IT methotrexate without cranial radiation therapy, Intrathecal chemotherapy alone.

Combination chemotherapy

The current induction regimens for patients with adult ALL include combination chemotherapy with prednisone, vincristine, and an anthracycline. Some regimens in a Cancer and Leukemia Group B (CALGB) study (CLB-8811), also add other drugs, such as asparaginase or cyclophosphamide. Current multiagent induction regimens result in complete response rates that range from 60% to 90%[11].

Imatinib mesylate

Imatinib mesylate is incorporated into the therapeutic plan for patients with Ph1-positive ALL. Imatinib mesylate, is an orally available inhibitor of the *BCR-ABL* tyrosine kinase, has been shown to have clinical activity as a single agent in Ph1-positive ALL[12].

In a study of imatinib from the Northern Italy Leukemia Group combined with chemotherapy idarubicin, vincristine, prednisone, and L-asparaginase, for patients with newly diagnosed, untreated Ph1-positive. For all patients who achieved remission, the intent was to proceed to allogeneic transplant when and if an HLA-matched donor could be identified. Patients lacking a donor received an autologous transplant. After completion of chemotherapy and transplant, all patients were to receive maintenance imatinib for as long as tolerated. After 20 patients had accrued to the imatinib arm, L-asparaginase was omitted from the induction regimen from both arms because of toxicity[13].

Supportive care

Similar outcomes have been observed for patients who received prophylactic platelet transfusions at a level of 10,000/mm^3 rather than at a level of 20,000/mm^3.

For neutropenic febrile patients, Careful instruction in personal hygiene and dental care, detecting early signs of infection are appropriate for all patients. Isolation facilities, including filtered air, sterile food, and gut flora sterilization, are not routinely indicated but may benefit transplant patients[14].

The incidence of platelet alloimmunization was similar among groups randomly assigned to receive one of the following from random donors[15]

- Unfiltered and Filtered Pooled platelet concentrates.
- Ultraviolet irradiated, pooled platelet concentrates.
- Filtered platelets obtained by apheresis.

Rapid marrow ablation with consequent earlier marrow regeneration decreases morbidity and mortality. White blood cell transfusions can be beneficial in selected patients with aplastic marrow and serious infections that are not responding to antibiotics.

Special Considerations for B-Cell and T-Cell Adult ALL

Two additional subtypes of adult ALL need special considerations. B-cell ALL - which expresses surface immunoglobulin and cytogenetic abnormalities such as t (8;14), t(2;8), and t(8;22), not usually cured with typical ALL regimens.

Aggressive brief-duration high-intensity regimens, including those previously used in CLB-9251 (NCT00002494), that are similar to those used in aggressive non-Hodgkin lymphoma displayed higher response rates and cure rates[16]. Similarly, T-cell ALL, including lymphoblastic lymphoma, has shown high cure rates when treated with cyclophosphamide-containing regimens.

Bortezomib (Velcade, formerly PS-341)

First proteasome inhibitor approved by the US FDA for the treatment of newly diagnosed multiple myeloma and relapsed/refractory multiple myeloma and mantle cell lymphoma. Mechanisms of Bortezomib anticancer activity are still not completely

understood, it is a new treatment option for patients with refractory or relapsed ALL, particularly when used in combination with conventional chemotherapy or targeted agents.

Bortezomib may enhance antileukemic activity when used in combination with chemotherapy or targeted agents. In a phase-I study, the TACL consortium reported that the combination of bortezomib (1.3 mg/m^2) with vincristine, dexamethasone, pegylated L-asparaginase and doxorubicin is active with acceptable toxicity in pretreated pediatric patients with relapsed ALL[17]. A study by Lancet et al. in Phase I Clinical trial also reported combination therapy with bortezomib and the farnesyltransferase inhibitor tipifarnib is well tolerated and produces modest antileukemic clinical activity in patients with ALL[18].

Inhibition of Notch1-NFκB Signaling Pathway in T-ALL

Aberrant NF-κB regulation has been observed in many cancers of both solid and hematopoietic malignancies. A study by Guzman et al demonstrated that human AML stem cells also express an active form of NF-κB. Expression of NF-κB in both AML and ALL cells and also represents a striking biologic distinction between leukemic and normal tissue. Taken together, these results indicate that NF-κB plays a critical role in the survival of leukemia cells including leukemic stem cells[19].

Previous studies reported that bortezomib can overcome chemo-resistance and restore sensitivity to specific agents, including doxorubicin, melphalan and dexamethasone. A possible mechanism for the chemosensitizing activity of bortezomib is the ability of NF-κB to promote resistance to these agents in MM cell lines. In addition, a patient of T-ALL, who was resistant to conventional chemotherapy, achieved second remission following treatment with a combination of bortezomib, dexamethasone and doxorubicin, and the binding activity of NF-κB-DNA in his bone marrow was strikingly reduced[20].

Previous reports also demonstrated that activating mutations in Notch1 are present in most individuals with human T-ALL and in mouse models of T-ALL. The Notch1 signaling pathway plays a critical role in promoting many steps of T cell development and aberrant Notch1 signaling is a major oncogenic event in the pathogenesis of T-ALL. These give a strong rationale for targeted therapies that interfere with Notch1 signaling in human T-cells[22].

Restoration of Expression of FoxO3 for Ph Chromosome-Positive ALL Patients

The Ph chromosome results from a reciprocal translocation between chromosomes 9 and 22 (t [9, 22] [q34; q11]), which produces a fusion gene on chromosome 22, namely, the breakpoint cluster region-Abelson leukemia viral proto-oncogene (BCR-ABL). Approximately one quarter of adult ALL expresses the oncogenic protein BCR-ABL however, it occurs in only 3-5% of pediatric cases[23]. Recently, Ph chromosome-positive ALL children and adolescents are considered one of the poor-risk subgroups of ALL patients. As a result of its elevated tyrosine kinase activity, BCR-ABL activates a multitude of signaling pathways, including the Ras, PI3-K/Akt, JAK/STAT and NF-κB signaling pathways, some of which may be crucial for its leukemogenic activity.

The study by Jagani *et al*. proposed that BCR-ABL stimulates the proteasome-dependent degradation of members of the forkhead family of tumor suppressors *in vitro*, in an *in vivo* animal model and in samples from patients with BCR-ABL-positive chronic myelogenous leukemia or ALL. Bortezomib treatment of BCR-ABL-transduced leukemic mice restored normal expression of FoxO3a and its targets TRAIL and Bim. Their study also reported that FoxO3 is significantly downregulated within lymphoblasts of Ph-positive ALL, but not Ph-negative ALL, and the Ph-positive ALL patient who was treated with bortezomib achieved full molecular and cytogenetic remission and restoration of expression of FoxO3 in response to the drug[24]. These results support the fact that FoxO3 is attenuated in BCR-ABL-mediated disease and may be utilized as a potential diagnostic biomarker. Bortezomib treatment led to the inhibition of BCR-ABL-induced suppression of FoxO proteins and their proapoptotic targets, thereby providing novel insights into the molecular effects of proteasome inhibitor therapy (Figure No.1).

ACUTE MYELOGENOUS LEUKEMIA (AML)

Symptoms[25]

The main symptoms are:

- Pale look and feeling tired and breathless – mostly due to anemia caused by reduction in RBCs.
- Prone to more infection than usual – Due to lack of WBCs.
- Unusual bleeding caused by very few platelets - bruises may appear without any injury, heavy periods in women, bleeding gums, nose bleeds and blood spots or rashes on the skin.
- Feeling Generally Unwell And Run Down.
- Having a fever and sweats, which may be due to an infection or the leukaemia itself.

Other Less Common Symptoms

Caused by a build-up of leukaemia cells in a particular area of the body. Your bones might ache, due to pressure from a build-up of immature cells in the bone marrow. You might also notice raised, bluish-purple areas under the skin due to leukaemia cells in the skin, or swollen gums caused by leukaemia cells in the gums.

Occasionally, a person has no symptoms and the leukaemia is discovered during a routine blood test.

Symptoms may appear over a few weeks, and people often feel ill quickly. Physician should be contacted immeditely if any of the above symtoms arise.

DIAGNOSTICS

Morphology

A bone marrow aspirate is a diagnostic work-up of a patient with suspected AML. The panel considers a marrow trephine biopsy optional, but only on patients with a dry tap (punctio sicca).

May-Grünwald-Giemsa or a Wright-Giemsa stain

Blood and marrow smears are morphologically examined using a May-Grünwald-Giemsa or a Wright-Giemsa stain. It is recommended 200 leukocytes on blood smears and 500 nucleated cells on marrow smears be counted, with the latter containing spicules. For a diagnosis of AML, a marrow or blood blast count of 20% or more is required, except for AML with t(15;17), t(8;21), inv(16) or t(16;16), and some cases of erythroleukemia. Myeloblasts, monoblasts, and megakaryoblasts are included in the blast count. In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes are counted as blast equivalents[26].

Countries still rely more on cytochemistry to identify lineage involvement rather than on immunophenotyping (usually by flow cytometry), using Sudan Black B (SBB) or myeloperoxidase (MPO) and nonspecific esterase (NSE) stains.

Detection of MPO, if present in ≥ 3% of blasts, indicates myeloid differentiation. Though its absence does not exclude a myeloid lineage because early myeloblasts and monoblasts may lack MPO. SBB staining parallels MPO but is less specific. Diffuse cytoplasmic activity is displayed by NSE stains in monoblasts, when usually > 80% positive and monocytes when usually > 20% positive. A periodic acid-Schiff (PAS) stain may show large globules of PAS positivity. Iron stains may allow for the detection of iron stores, normal sideroblasts, and ring sideroblasts.

Immunophenotyping

Immunophenotyping using multiparameter flow cytometry (usually at least 3 to 4 color) is used to determine lineage involvement of a newly diagnosed acute leukemia by various markers and stages as mentioned below in Table No.1[26].

For most markers, a commonly used criterion is 20 % or more of leukemic cells expressing the marker, whereas for selected markers (eg, cytoplasmic CD3, MPO, TdT, CD34, CD117) a lower cutoff has been applied (10%)[27].

Immunophenotyping is required to establish the diagnosis of AML with minimal differentiation, acute megakaryoblastic leukemia, and acute leukemias of ambiguous lineage. AML with minimal differentiation is an AML without morphologic and cytochemical evidence of myeloid differentiation[28]. Most cases express early hematopoiesis-associated antigens (eg, CD34, CD38, and HLA-DR) and lack most markers of myeloid and monocytic maturation; while MPO is negative by cytochemistry, detection of intracytoplasmic MPO antigens may be positive by flow cytometry in at least a fraction of blasts. Acute

megakaryoblastic leukemia is leukemia with 20% or more blasts of which 50% or more are of megakaryocytic lineage;

Some AMLs displaying genetic abnormalities recurrently are associated with characteristic immunophenotypic features. For example, AMLs with t(8;21) expresses the lymphoid markers CD19 or, to a lesser extent, CD7; they may also express CD56; AMLs with inv(16) frequently express the T lineage–associated marker CD2; and AMLs with *NPM1* mutation typically have high CD33 but absent or low CD34 expression[29].

Cytogenetics

Conventional cytogenetics analysis is a mandatory component in the diagnostic evaluation of patients with acute leukemia. Chromosome abnormalities are detected in approximately 55% of adult AML[30].

About Seven recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category "AML with recurrent genetic abnormalities." Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of "AML with myelodysplasia-related features" when 20% or more blood or marrow blasts are present.

About a minimum of 20 metaphase cells analyzed from bone marrow is considered as a mandatory to establish the diagnosis of a normal karyotype, and recommended to define an abnormal karyotype. Abnormal karyotypes may be diagnosed from the blood specimens.

Molecular cytogenetics

Methanol/acetic acid-fixed cell pellets are to be stored, in case if cytogenetic analysis diagnostic failure happens, (FISH) Fluorescence In Situ Hybridization is an option for detection of gene rearrangements, such as *RUNX1-RUNX1T1*, *CBFB-MYH11*, *MLL* and *EVI1* gene fusions, or loss of chromosome 5q and 7q material[31]. FISH is frequently necessary to identify *MLL* fusion partners in 11q23 translocations.

Molecular genetics

A marrow (and blood) specimen routinely should be taken for molecular diagnostics. Ideally, DNA and RNA should be extracted and stored as viable cells; RNA extraction should be a priority, if cell numbers are limited because RNA is most suitable for molecular screening for fusion genes and leukemia-associated mutations.

Molecular diagnosis by reverse transcriptase-polymerase chain reaction (RT-PCR) for the recurring gene fusions, such as, *DEK-NUP214*, *RUNX1-RUNX1T1*, *CBFB-MYH11* and *MLLT3-MLL* can be useful in certain circumstances. RT-PCR, for which standardized protocols were published by the BIOMED-1 group is an option to detect these rearrangements, if chromosome morphology is of poor quality, or if there is typical marrow morphology but the suspected cytogenetic abnormality is not present[32].

Somatically acquired mutations have been identified in several genes, for example, the *NPM1* gene,[33] the *FLT3* gene, the *CEBPA* gene, the myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, *Drosophila*) (*MLL*) gene, the neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*) gene, the Wilms tumor 1 (*WT1*) gene, the v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*) gene, the runt-related transcription factor 1 (*RUNX1*) gene, the test oncogene family member 2 (*TET2*) gene, and the isocitrate dehydrogenase 1 (NADP+), soluble (*IDH1*) gene. The frequencies of these gene mutations vary among cytogenetic groups[34].

AML with mutations in *NPM1* or *CEBPA* have been incorporated in the WHO classification as provisional entities. Screening for these 2 markers as well as for *FLT3* mutations should be done in clinical trials. While testing for *NPM1*, *CEBPA*, and *FLT3* is currently not considered mandatory outside clinical trials, the panel recommends that these 3 mutations be analyzed at least in patients with cytogenetically normal AML (CN-AML) who will receive treatment other than low-dose chemotherapy or best supportive care.

Genome-wide studies

Recent progress in genomics technology has resulted in the identification of novel genetic abnormalities and holds the scope of making the systematic characterization of cancer genomes feasible[33]. For example, gene- and micro RNA-expression profiling have been very valuable for the discovery and

classification of novel leukemia subgroups and of prognostic signatures.

The introduction of genome-wide single nucleotide polymorphism (SNP) - based mapping arrays, providing both the copy number and allele-specific information, led to identification of a novel mechanism involved in the pathogenesis of AML, that is, uniparental disomy (UPD)[34]. Acquired UPD is due to mitotic recombination event and may render a cell homozygous for a pre-existing mutation located in the affected genomic region. The power of SNP genotyping as a tool for gene discovery is shown by several recent studies[35].

Biobanking

It is strongly recommend within the clinical trials to store patients' pretreatment leukemic marrow and blood within a biobank. A prerequisite for biobanking is the patient's informed consent that ideally should allow a broad spectrum of correlative laboratory studies that also include analysis of germline DNA. Pretreatment samples should include nucleic acid (DNA and RNA, stored at -80°C) and viable cells (stored at -196° C). For further optional storage, we advise saving germline DNA (eg, from a buccal swab, frozen cell pellets, skin biopsy, or sputum), a plasma sample, and a methanol/acetic acid–fixed cell pellet (from cytogenetic analysis) from various time points during and after treatment (ie, at the time of complete remission [CR], at relapse; and for MRD monitoring at defined time points during treatment and follow-up), stored under appropriate conditions[36].

Other diagnostic tests

Additional diagnostic tests and procedures in the initial work-up of a patient with AML are given in Table No.2 below.

a. Including race or ethnicity, family history, prior exposure to toxic agents, prior malignancy, therapy for prior malignancy, information on smoking.
b. *Biochemistry*: glucose, sodium, potassium, calcium, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase, bilirubin, urea, total protein, uric acid, total cholesterol, total triglycerides, creatinine phosphokinase (CPK). *Coagulation tests*: prothrombin time (PTT), international normalized ratio (INR) where indicated, activated partial thromboplastin time (aPTT). *Urine analysis*: pH, glucose, erythrocytes, leukocytes, protein, nitrite.
c. In women with a childbearing potential.
d. Required in patients with clinical symptoms suspicious of central nervous system involvement; patient should be evaluated by imaging study for intracranial bleeding, leptomeningeal disease, and mass lesion; lumbar puncture considered optional in other settings (eg, high WBC).
e. Pretreatment leukemic bone marrow and blood sample; for further optional storing see section 4.7.
f. Mandatory in patients with a dry tap (punctio sicca).
g. Should be performed if chromosome morphology is of poor quality, or if there is typical morphology but the suspected cytogenetic abnormality is not present.
h. Cryopreservation to be done in accordance with the wish of the patient.
i. HLA typing and CMV testing should be performed in those patients eligible for allogeneic stem cell transplantation.
j. Biobanking should also be performed in general practice if at all possible.
k. Strongly encouraged in AML with normal karyotype.

RESCENT ADVANCES - AML

Treatment of Minimal Residual Disease after Chemotherapy

Recurrence is inevitable in the majority of the patients without allogeneic transplantation. It is only possible to achieve complete remission by a series of initial chemotherapies in about 80% of AML patients,. It has been reported that leukemia stem cells are resistant to chemotherapy and that it may be an important reason why it is difficult to eradicate AML cells in the majority of patients[37].

Antigens Associated with AMLs

Recent studies have identified several promising AML antigens suitable for targets of immunotherapy. One of the most promising AML-associated antigens is Wilms' tumor 1 (WT1). It was originally reported that HLA-A∗2402- and HLA-A∗0201- restricted WT1 peptides induce cytotoxic T lymphocytes (CTLs) that kill WT1-expressing leukemic cells but not normal progenitor cells. WT1 is a transcription factor that plays an important role in leukemogenesis and thus it is less probable that the expression of WT1 is lost[38].

Proteinase 3 is a myeloid cell-restricted serine protease expressed in great quantities in azurophilic granules and is a promising myeloid leukemia-associated antigen. It was originally reported that HLA-A∗0201-restricted proteinase 3 peptides induces CTLs that preferentially kills myeloid leukemia cells sparing normal marrow cells. Proteinase 3 has also been shown to be immunogenic, as proteinase-3-specific CTLs are induced in a substantial fraction of myeloid leukemia patient's *invivo*[39].

Other than WT1 and proteinase 3, the receptor for hyaluronic-acid-mediated motility (RHAMM/CD168), Aurora-A human telomerase reverse transcriptase (hTERT) and preferentially expressed antigen in melanoma (PRAME), have been reported as potentially useful AML-associated antigens. Notably, WT1 and Aurora-A are reported to be expressed in leukemia stem cells and may thus be suitable targets to eradicate AML[40].

Active Immunization - Methods of Antigen-Specific Immunotherapy for AML

Antigen-specific immunotherapies can be largely divided into two categories:

- Active immunization - antigens of tumor are injected to provoke antigen-specific immune responses *invivo*.
- Adoptive T cell therapy - There are mainly the following three ways reported for AML: p secreting tumor vaccines, eptide vaccines, granulocyte-macrophage colony-stimulating-factor- (GM-CSF) and dendritic cell (DC) vaccines.

Peptide based Vaccines

WT1 peptide vaccines have been actively pursued. Oka et al. have first reported a clinical trial of HLA-A∗2402-restricted WT1 peptide vaccination for malignancies including 12 AML patients. Rezvani *et al*. reported a clinical trial of combined administration of HLA-A∗0201-restricted WT1 and proteinase 3 peptides to 8 patients with myeloid malignancies Immune responses to both WT1 and proteinase 3 were detected after a single vaccination in all the patients, suggesting expansion of preexisting memory CD8+ T cells. However, the responses were short-lived and became undetectable after 4 weeks, indicating the necessity of repetitive boost injection.

Maslak et al. reported a clinical trial of a novel combination of WT1 peptide vaccination for 9 AML patients. They used a mixture of 4 peptides; one is an HLA-A∗0201-restricted heteroclitic peptide that has higher affinity to the HLA class I molecule than a native peptide, and three are long peptides that bind to multiple HLA-DRB1 haplotypes[41-44].

Tumor Vaccines that secrete GM-CSF

In tumor cells, random mutationa are expected to generate many individually specific antigens that may induce multivalent antitumor immune responses of both CD4+ and CD8+ T cells. Thus, the whole autologous tumor cell vaccination is a viable option as long as a sufficient number of tumor cells are harvested in advance.

A mixture of killed autologous leukemia cells and a GM-CSF gene-transduced K562 leukemia cell line was used for vaccination in combination with primed T cells after autologous stem cell transplantation for 54 patients with AML[45].

DC Vaccines

DCs that are generated *ex - vivo* from monocytes or CD34+ progenitor cells are modified to present tumor antigens and are injected. It has also been reported that AML cells can be differentiated into DCs and they can be injected. In the first DC vaccination for AML, Fujii *et al*. used CD34+ progenitor cell-derived DCs pulsed with autologous leukemic cellswhich are in combination with primed T cells for 4 relapsed patients after allogeneic stem cell transplantation[46].

It is recently reported in two clinical studies of MoDC-based immunotherapy for AML at morphologic complete remission in elderly patients. In one study, MoDCs was admisinstered to elderly patiemts that engulfed autologous apoptotic leukemic cells to 4 patients[47].

Collectively, these studies indicate that MoDC-based immunotherapy is immunogenic even in elderly patients with AML after remission-inducing chemotherapy and require further study of this strategy.

Methods for Antigen-Specific Immunotherapy for AML: Adoptive T Cell Therapy

Immune competence of cancer patients decides active immunization of patients. However, tumor antigen-specific T cells are sometimes non-functional or deactivated in the presence of tumor cells in vivo in cancer patients. In addition, chemotherapy and immunosuppressive factors from tumor cells may undermine antitumor immunity in cancer patients[48]. Based on these ideas, adoptive transfer of tumor-specific T cells is actively pursued.

Tumor-specific adoptive T cell therapy was initially developed by expanding tumor-infiltrating lymphocytes from melanoma lesions in vitro[49]. However, complicated procedures and difficulty in timely preparation of a sufficient number of cytotoxic T lymphocytes (CTLs) preclude generalization of this strategy.

Adoptive T Cells Transfer with Transgenic TCR

The first clinical trial of TCR-transduced T cell transfer was performed for advanced melanoma patients by Rosenberg's group, using HLA-A∗0201-restricted MART-1, gp100, NY-ESO-1, and p53 as targeted antigens[50]. The transduced T cells were administered after a therapy with lymphodepleting regimen of fludarabine and cyclophosphamide. 2out of 17 patients achieved partial remission. Therapeutic effect absence in most of the cases may be due to the failure of the infused cells to accumulate into the tumor or to exert their effector function in the immunosuppressive tumor microenvironment.

In recent study by the same group, a retrovirus encoding the high avidity murine CEA-reactive TCR was used to transduce peripheral blood lymphocytes from 3 HLA-A∗0201+ patients with metastatic colorectal cancer[51]. All patients experienced profound decreases in serum CEA levels. However, a severe transient inflammatory colitis was induced in all 3 patients. These studies indicate excellent antitumor activity as well as destructive power of highly avid T cells against normal tissues, suggesting the importance of careful assessment of possible damage to normal tissues that share the target antigen with tumor cells.

Adoptive Transfer of T Cells with Transgenic CAR

A CAR contains an extracellular antigen-binding domain, a transmembrane region, and a signaling endodomain. The extracellular domain is a single chain variable fragment (scFv) derived from a tumor-specific monoclonal antibody.

There are two advantages of using an antibody-derived domain for antigen recognition.

- Antibodies are not dependent on MHC presentation.
- Antibodies bind antigens with much greater affinity than TCRs, leading to the formation of a more stable immunological synapse.

CARs are grouped into three generations with progressive increase in costimulatory activity. These differ primarily in the structure of the signaling endodomain.

First-generation CARs

These contain a single signaling unit derived from the CD3 chain alone, which transmits a signal inadequate to fully activate T cells.

In second-generation CARs

The CD28 intracellular domain is inserted proximal to the CD3 endodomain to enhance the stimulatory effects of the CAR. This further motivated addition of other signaling sequences from costimulatory molecules such as 4-1BB and OX40 in third-generation ARs. A complete response was observed in a patient with follicular lymphoma who received T cells transduced with a second-generation anti-CD19 CAR[52].

Table No.1: Expression of cell-surface and cytoplasmic markers for the diagnosis of acute myeloid leukemia and mixed phenotype acute leukemia

S.No	EXPRESSION OF MARKERS FOR DIAGNOSES	
Diagnosis of Acute Myeloid Leukemia (Aml)*		
1	Precursor stage	CD34, CD38, CD117, CD133 and HLA-DR
2	Granulocytic markers	CD13, CD15, CD16, CD33, CD65, and cytoplasmic myeloperoxidase (cMPO)
3	Monocytic markers	Nonspecific esterase (NSE), CD11c, CD14, CD64, lysozyme, CD4, CD11b, CD36, and NG2 homologue‡
4	Megakaryocytic markers	CD41 (glycoprotein IIb/IIIa), CD61 (glycoprotein IIIa), and CD42 (glycoprotein 1b)
5	Erythroid marker	CD235a (glycophorin A)
Diagnosis of Mixed Phenotype Acute Leukemia (Mpal)†		
1	Myeloid lineage	MPO or evidence of monocytic differentiation (at least 2 of the following: NSE, CD11c, CD14, CD64, and lysozyme)
2	B-lineage	CD19 (strong) with at least one of the following: CD79a, cCD22, CD10, or CD19 (weak) with at least 2 of the following: CD79a, cCD22, and CD10
3	T-lineage	cCD3, or surface CD3

Table No.2: Test/procedures in the initial work-up of a patient with AML[36]

S.No	Test/procedure	General practice	Clinical trial
	Tests to establish the diagnosis		
1	Complete blood counts and differential count	Yes	Yes
2	Bone marrow aspirate	Yes	Yes
3	Bone marrow trephine biopsy	Optional[f]	Optional[f]
4	Immunophenotyping	Yes	Yes
5	Cytogenetics	Yes	Yes
6	RUNX1-RUNX1T1, CBFB-MYH11, PML-RARA, or other gene fusion screening	Optional[g]	Optional[g]
7	**Additional tests/procedures at diagnosis**		
8	Demographics and medical history[a]	Yes	Yes
9	Performance status (ECOG/WHO score)	Yes	Yes
10	Analysis of comorbidities	Yes	Yes
11	Biochemistry, coagulation tests, urine analysis[b]	Yes	Yes
12	Serum pregnancy test[c]	Yes	Yes
13	Information on oocyte and sperm cryopreservation	Optional[h]	Optional[h]
14	Eligibility assessment for allogeneic HSCT	Yes[i]	Yes[i]
15	Hepatitis A, B, C; HIV-1 testing	Yes	Yes
16	Chest x-ray, 12-lead ECG; echocardiography (on indication)	Yes	Yes
17	Lumbar puncture[d]	No	No
18	Biobanking[e]	Optional[j]	Yes
19	**Prognostic/predictive marker assessment**		
20	NPM1, CEBPA, FLT3 gene mutation	Optional[k]	Yes
21	WT1, RUNX1, MLL, KIT, RAS, TP53, TET2, IDH1 gene mutation	No	Investigational
22	ERG, MN1, EVI1, BAALC gene expression	No	Investigational
23	Detection of minimal residual disease	No	Investigational

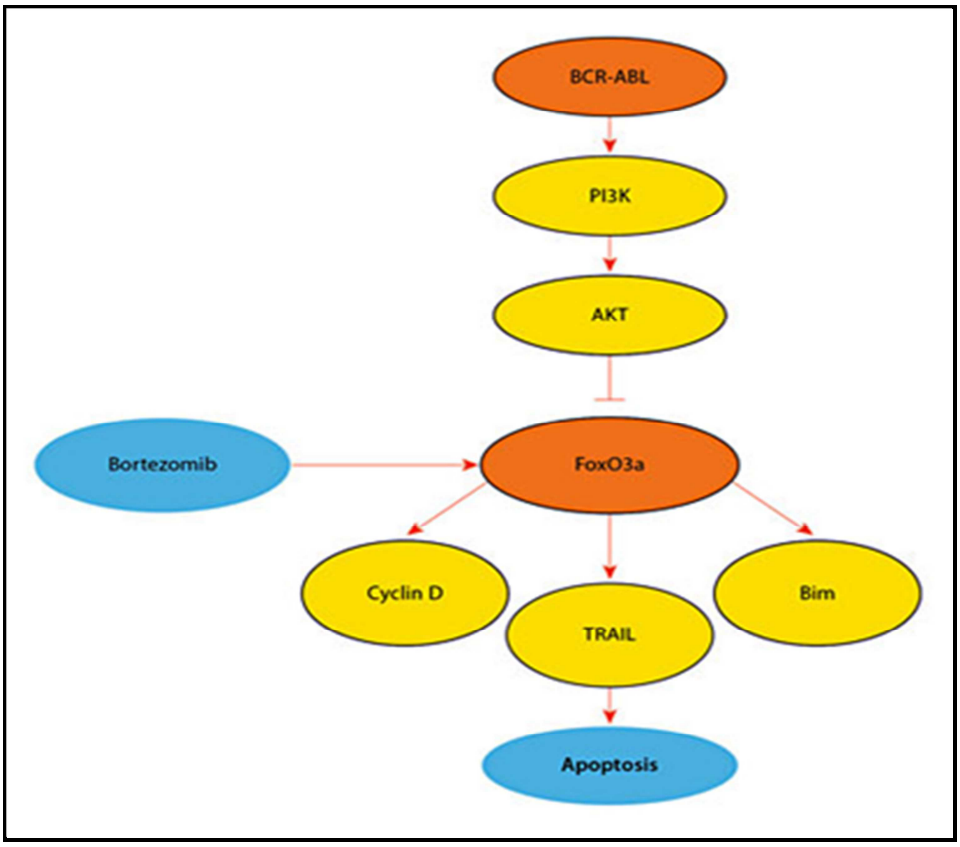

Figure No.1: Inhibition of BCR-ABL-induced suppression of FoxO proteins and their proapoptotic targets in Ph + ALL patients with Bortezomib Treatment

CONCLUSION

Chemoimmunotherapy is the standard first-line option approach for CLL, the most common leukemia observed in adults. Treatment is initiated when the disease becomes symptomatic, and survival is high following treatment. Lot of advanced treatments as mentioned in the review is available for the treatment of Leukemia.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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