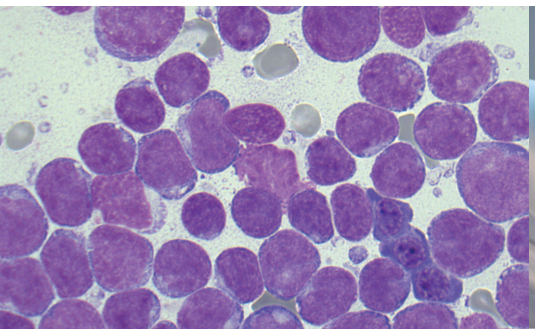
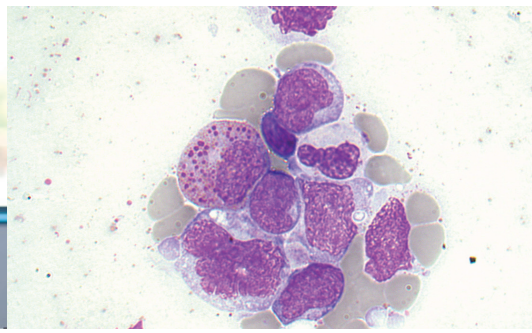
HNHCP
Haematology Nurses & Healthcare Professionals Group





Haematology Nurses and Healthcare Professionals (HNHCP)

Acute Leukemia in Adults: A Resource for Healthcare Professionals

Dear Colleague

It is with great pleasure that the Haematology Nurses and Healthcare Professionals (HNHCP) group presents the learning programme „Acute Leukemias in Adults: A Resource for Healthcare Professionals".

A faculty of specialist nurses working in the field of haematology/oncology, haematologists, and patient advocates have collaborated to develop this comprehensive programme dedicated to acute Leukemia.

This programme features topics relevant to the multidisciplinary team approach to caring for patients with acute Leukemia and their caregivers. Nurses, other allied healthcare professionals and patient organisations play an important role in this process and the HNHCP is excited to share with you the most current information and up-to-date recommendations for addressing the unique aspects of addressing the patient's needs throughout the disease continuum.

The Acute Leukemia Resource for Healthcare Professionals Program was made possible by an educational grant from AMGEN (Europe) GmbH, Jazz Pharmaceuticals, Novartis Pharma Switzerland AG, Roche Pharma AG Switzerland and Servier.

On behalf of the Haematology Nurses and Healthcare Professionals Group and the faculty who worked on this initiative, we hope that the Acute Leukemia Resource will be of value to you in your care of patients with acute Leukemia.

Sincerely,

Erik Aerts

President

Haematology Nurses and Healthcare Professionals Group

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Acute Leukemia: A Resource for Healthcare Professionals is also available online at

www.hemcare.org

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Contents

Quick Facts

- Acute Leukemia is characterized as a neoplastic proliferation of either the lymphoid (ALL) cell line or myeloid (AML) cell line
- Older age, exposure to certain chemicals and certain genetic syndromes are associated with a higher probability of developing acute Leukemia
- The signs and symptoms of Leukemia result from a lack of mature blood cells: As the number of Leukemia cells (blasts) fills the bone marrow space, the number of normal cells in the bone marrow decreases
- While deaths from acute Leukemia have shown a decline, the incidence of acute Leukemia has steadily increased, most likely due to demographic changes and the association between older age and the development of acute Leukemia
- Translocations of genes are the most common type of chromosome change that can lead to Leukemia

Module I: Understanding Acute Leukemia

INTRODUCTION: Understanding Acute Leukemia

Leukemia is a group of malignant disorders affecting the blood and blood-forming tissues in the bone marrow, lymphatic system and spleen. Acute Leukemia is a malignant neoplastic disease that arises from either the lymphoid cell line (acute lymphoblastic/lymphocytic/lymphoid Leukemia, or ALL) or from the myeloid cell line (acute myeloid/myelogenous/myelocytic Leukemia, or AML). Leukocytosis, an increased white blood cell count, is a normal response to infection but when leukocytosis becomes chronic or progressively elevates without obvious cause, then it may indicate malignancy. In acute Leukemia, there is an uncontrolled proliferation of malignant, immature cells (known as blasts) of the hematopoietic system.

The two primary types of acute Leukemia are acute lymphoblastic Leukemia (ALL) and acute myeloid Leukemia (AML) sometimes referred to as acute nonlymphoblastic Leukemia (ANLL). Acute Leukemia is a proliferation of immature bone marrow-derived cells (blasts) that may also involve peripheral blood or solid organs. While the percentage of bone marrow blast cells required for a diagnosis of acute Leukemia was set at 30% or more (Abdul-Hamid 2011), the blast cell count has been lowered to 20% and a minimum blast cell percentage is not required when certain morphologic and cytogenetic features are present [**see Module 2, Establishing a Diagnosis of Acute Leukemia**].

The traditional French-American-British (FAB) classification of ALL and AML is based on morphology and cytochemical staining of blasts; the European Group for the Immunological Classification of Leukemias (EGIL) now proposes classifying acute Leukemia on the basis of immunophenotype alone. The WHO classification schema integrates information on molecular, diagnostic and cytogenetic information. The classification of acute Leukemia [**see Module 2**] is an important step in the diagnostic process as not only does this information provide insight into the cytogenetic abnormalities causing the disease, but classification also provides information to determine patient treatment and prognosis.

Overview of Normal Blood Cell Production

Bone is made up of compact bone, spongy bone, and bone marrow (**Fig. 1**). Compact bone makes up the outer layer of the bone. Spongy bone is found mostly at the ends of bones and contains red marrow. Bone marrow is found in the center of most bones and has many blood vessels. There are two types of bone marrow: red and yellow. Red marrow contains blood stem cells that can become red blood cells, white blood cells, or platelets. Yellow marrow is made mostly of fat.

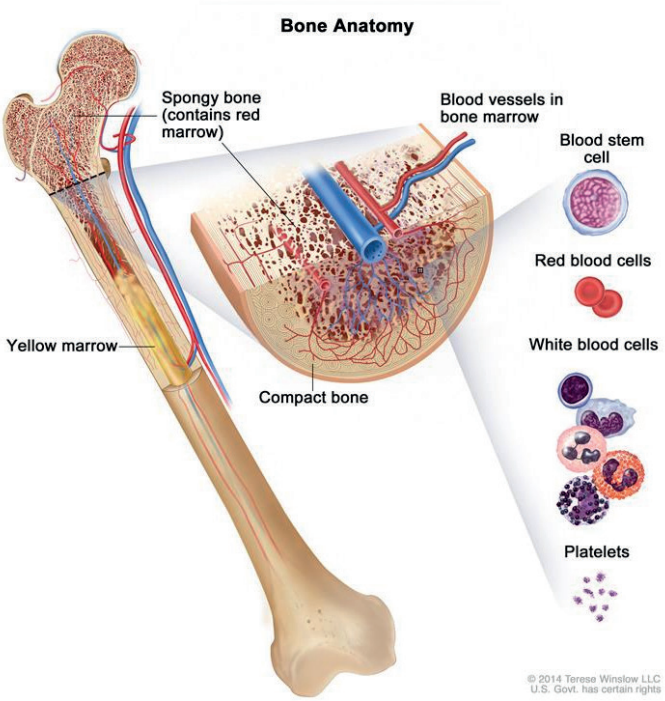

Figure 1: Bone anatomy.

Normally, the bone marrow produces blood stem cells (immature cells), the cells from which all blood cells are formed. Blood stem cells differentiate into two types of progenitor cells: myeloid and lymphoid progenitor cells. Progenitor cells form into blast cells, which are immature

blood cells. A lymphoid progenitor cell differentiates into a lymphocyte or white blood cell. Lymphocytes, granulocytes and monocytes are all white blood cells. Lymphocytes include natural killer cells (NK cells), B cells and T cells, which aide in the body's immune response. Common myeloid progenitor cells develop into red blood cells (erythrocytes), platelets and monocytes (granulocytes), which include neutrophils, eosinophils and basophils (**Fig 2**).

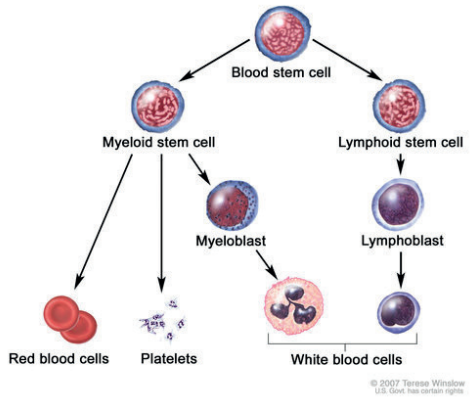

Figure 2: Blood cell development. A blood stem cell makes two types of progenitor cells: lymphoid progenitor cells form into lymphocytes (white blood cells) and myeloid progenitor cells form into red blood cells, platelets and granulocytes (white blood cells).

Pathophysiology

The genetic aberrations resulting in the blockage of differentiation and uncontrolled proliferation of the precursor cells (blasts) may occur at different developmental stages, including the pluripotential stem cells and the progenitors committed to the lymphoid or myeloid lineages. The rapid proliferation of the leukemic blasts, along with a reduction in their ability to undergo programmed cell death (apoptosis), results in their accumulation in the bone marrow, the blood, and, frequently, the spleen and liver.

ALL is a malignant transformation and proliferation of lymphoid progenitor cells (lymphoblasts) and AML is a malignant transformation of myeloid precursors (myeloblasts, monoblasts, erythroblasts or megakaryoblasts).

The onset of the acute forms of Leukemia is often abrupt, within weeks, and death may occur within weeks to months if treatment is not implemented. The signs and symptoms of Leukemia result from a lack of mature blood cells: As the number of Leukemia cells (blasts) fills the marrow space, the number of normal cells in the bone marrow decreases. These non-functional malignant cells proliferate at the expense of healthy cells resulting in reduced numbers of platelets, erythrocytes (red blood cells [RBCs]) and neutrophils (white blood cells [WBCs]. Reduced numbers of platelets, red blood cells and neutrophils in the peripheral blood system may lead to hemorrhages, anemia, and easy susceptibility to infections of any type, respectively. Hence, the clinical presentation of ALL and AML is similar.

In addition to the proliferation of blasts in the bone marrow, cells may proliferate in the liver and spleen and may infiltrate other organs such as the meninges, gums, lymph nodes and skin. Central nervous system involvement is more frequent in ALL than in AML.

Risk Factors

There is a higher probability of developing ALL in the presence of the following risk factors:

- Exposure to high levels of radiation
- Age older than 50 as well as in children
- Past treatment with chemotherapy or radiation therapy
- Exposure to high levels of radiation in the environment
- Certain genetic disorders, such as Down syndrome
- Exposure to certain chemicals such as benzene
- Viral infections (eg, human T lymphotropic virus 1 and 2, Epstein Barr virus) can rarely cause certain forms of ALL; this is seen mainly in regions where such infections are common, such as Asia and Africa

There is a higher probability of developing AML in the presence of the following risk factors:

- Exposure to high levels of radiation in the environment or previous cancer treatment with radiation therapy
- Older age
- Smoking
- Exposure to certain chemicals such as benzene
- Previous chemotherapy treatment, especially with alkylating agents and topoisomerase II inhibitors
- History of chronic myeloproliferative disorders such as polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis
- Certain genetic syndromes such as Fanconi anemia, Down syndrome

An increased risk of therapy-related AML (called t-AML) is associated with prior treatment with certain antineoplastic drugs, including alkylating agents and

topoisomerase II inhibitors and radiation therapy, and older age at treatment. Among autologous hematopoietic cell transplantation (HSCT) recipients, method of stem cell mobilization (priming with etoposide) and transplantation conditioning with total body irradiation are associated with an increased risk of t-AML (Bhatia 2013). The incidence of t-AML is higher among patients with certain primary tumors (breast, gynecologic cancers, lymphomas). The disease course of t-AML is generally progressive and may be more resistant to therapy than de novo cases of AML, due mostly to the adverse cytogenetic abnormalities present in t-AML. Further, clinical outcomes in patients with t-AML have been shown to be inferior compared to de novo cases (NCCN 2019b).

Acute Lymphocytic Leukemia (ALL)	
Estimated new cases of ALL in 2019 in the U.S.	5,930
% of all new cancer cases	0.3%
Estimated deaths in 2019	1,500
% of all cancer deaths	0.2%
Acute Myeloid Leukemia (AML)	
Estimated new cases of ALL in 2019 in the U.S.	21,450
% of all new cancer cases	1.2%
Estimated deaths in 2019	10,920
% of all cancer deaths	1.8%
Rates are age-adjusted and based on 2012-2016 cases and deaths (SEER, 2019)	

Incidence

Both ALL and AML are rare diseases. The number of new cases of Leukemia (all types) in the US in 2019 is estimated to be 61,780, representing 3.5% of all new cancer cases (SEER, 2019). The incidence of AML in Europe is approximately 3 to 4 cases per 100,000 per year (30,000 new cases each year) (Harmony Alliance, 2019). Whereas rates of new cases of AML have been rising on average 2.0% each year over the last 10 years, rates of ALL have been rising at a somewhat slower rate, 0.6%, each year (SEER, 2019).

ALL is most common in Hispanics and Whites and in children, adolescents and young adults (15 to 39 years of age). The median age at diagnosis for ALL is 15 years with 55.4% of patients diagnosed at younger than 20 years of age. In contrast, 28% of cases are diagnosed at 45 years or older and only approximately 12.3% of patients are diagnosed at 65 years or older (NCCN 2019a).

AML is more common in older adults and among men compared to women; the median age at diagnosis is 67 to 71 years, depending on the registry consulted, with 54% of patients diagnosed at 65 years or older (and approximately a third diagnosed at ≥75 years of age) (NCCN 2019b). Thus, as the population ages, the incidence of AML seems to be rising.

Acute promyelocytic Leukemia (APL) is a subtype of AML and accounts for 10% of AML cases. Its incidence is estimated to be 1/1,000,000 people in Europe. APL usually occurs in middle-aged adults and very rarely in pediatric patients. APL is characterized by arrest of leukocyte differentiation at the promyelocyte stage, due to a specific chromosomal translocation t(15;17) in myeloid cells.

Understanding the Role of Genomics in Acute Leukemia

The nucleus of a cell contains chromosomes, which are long strands of DNA tightly wrapped around proteins (**Fig. 3**). Genes are small pieces of DNA. Within a cell's DNA are coded instructions for building new cells and controlling the behavior of cells. Abnormal changes in genes can turn normal cells into cancer cells, which may behave differently from normal cells and, at times, also appear differently.

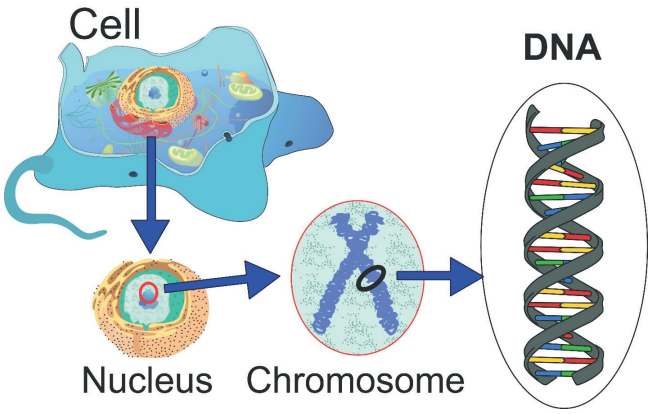

Figure 3: Genetic material in cells. Genetic changes that promote cancer can be inherited or acquired as the result of errors that occur as cells divide or from exposure to carcinogenic substances that damage DNA. Some changes affect just one unit of DNA, called a nucleotide in which one nucleotide may be replaced by another, or it may be missing entirely. Other changes involve larger stretches of DNA and may include rearrangements, deletions or duplications of long stretches of DNA.

The alteration in genes leads to their transformation into malignant cells by mechanisms which are only partially understood. At present, there are very specific techniques such as conventional cytogenetics, in situ hybridization or molecular biology techniques that make it possible to study the genes and chromosomes. In this way, alterations which help to make the diagnosis and classify the type of acute Leukemia may be detected and treatment may be administered on the basis of these findings [**see Module 2**]. In acute Leukemia it is thought that both genetic and environmental factors (for example, ionizing radiation or toxic substances such as derivatives of benzol and pesticides) and even infections (such as viral infections) may play a role in altering genes. In most cases it is not possible to discover the cause of the Leukemia. Although some genetic abnormalities are found in Leukemias, it is important to emphasize that acute Leukemias are infrequently hereditary.

Several types of genetic abnormalities can be found in acute Leukemia cells.

Translocations are the most common type of chromosome change that can lead to Leukemia. Translocation involves the exchange or transfer of fragments of genes to another chromosome (**Fig. 4**). The point on the chromosome where the break occurs can affect nearby genes – for example, it can turn on oncogenes or turn off genes that would normally aid in the process of cell maturity.

The most common translocation in ALL in adults is known as the Philadelphia chromosome, which is a swap of DNA between chromosomes 9 and 22, abbreviated as t(9;22). Many other, less common translocations, can occur as well, including those between chromosomes 4 and 11, t(4;11).

Deletions occur when part of a chromosome is lost (**Fig. 4**). This can result in the cell losing a gene that controls cell growth (tumor suppressor gene). Deletions are more common chromosomal changes in AML than in ALL.

An inversion is a chromosome rearrangement in which a segment of a chromosome is reversed end to end (**Fig. 4**). This occurs when a single chromosome undergoes breakage and rearrangement with itself. This can result in the loss of a gene (or genes) because the cell can no longer read its instructions. Gene inversion occurs more commonly in AML than in ALL.

Addition or duplication means there is an extra chromosome or part of a chromosome. This can lead to too many copies of certain genes within the cell. This can be a problem if one or more of these genes are oncogenes.

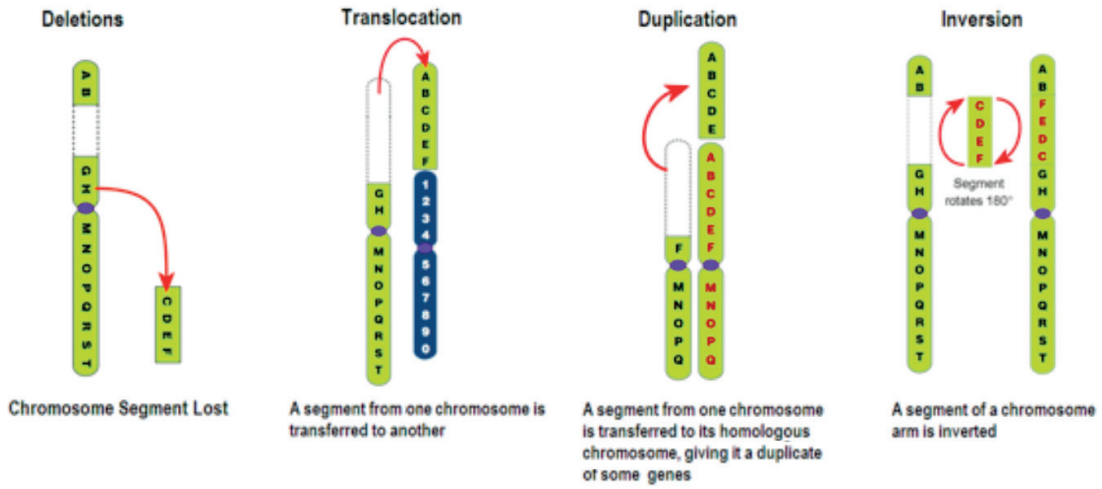

Figure 4. The four types of chromosomal mutations.

Future Perspectives

The HARMONY Alliance is collecting data across Europe on seven hematologic malignancies and working towards making comprehensive databases, data mapping tools and data analysis available to healthcare professionals and patient and societal organizations. Their goal is to provide a BigData Platform that will integrate and harmonize information on hematologic malignancies from > 100,000 patients. The data contained in the database will allow the assessment of new biomarkers, the analysis of genomes and the identification of relevant clinical outcomes.

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Quick Facts

- The initial evaluation of patients with acute Leukemia has two objectives: 1) characterize disease-specific factors, 2) identify patient-specific factors. Both evaluations provide important information for treatment decisions and risk stratification
- Anemia, thrombocytopenia and neutropenia are common clinical manifestations of acute Leukemia and result from clonal proliferation of myeloblasts (in AML) and lymphoblasts (in ALL), which replace normal bone marrow cells
- The diagnosis of AML and ALL is made based on the presence of ≥ 20% blasts in the marrow or peripheral blood
- In AML, the presence of co-morbidities, older age, complex karyotype abnormalities, previous chemotherapy or radiation exposure and history of auto immune disorders or antecedent hematologic disorders are associated with increased risk
- In ALL, patient age, WBC count, immunophenotypic/cytogenetic subtype and the presence of CNS disease are associated with increased risk

Module II: Establishing a Diagnosis of Acute Leukemia as the Basis for Treatment Decisions

A. Introduction
    1. Overview of clinical presentation
    2. Overview of common diagnostic practices
    3. Other assessments and workup practices
    4. Measurable residual disease
B. Acute Myeloid Leukemia
    1. Clinical presentation and physical findings
    2. Diagnostic workup
    3. Classification schema
    4. Prognostic factors and risk stratification
    5. Acute promyelocytic Leukemia
C. Acute Lymphocytic Leukemia
    1. Clinical presentation and physical findings
    2. Diagnostic workup
    3. Classification schema
    4. Prognostic factors and risk stratification
    5. ALL in adolescents and young adults
D. Future Perspectives in Acute Leukemia
References

Introduction

The initial workup and evaluation of acute Leukemia has become increasingly complex during the past decade due, in part, to the availability of new and technologically advanced laboratory techniques, particularly genetic studies (**Fig. 1**). These new techniques provide better characterization of acute Leukemia, which has nearly 50 distinct subtypes (Arber 2016). Integration of clinical data with results of morphologic, histologic, flow cytometry and cytogenetic and molecular diagnostic investigations are crucial to establish a comprehensive diagnosis and to guide treatment planning.

The initial evaluation of patients with acute Leukemia has two objectives: 1) characterize disease-specific factors based on karyotypic and molecular abnormalities, causative factors such as prior toxic exposure, which may provide prognostic information; 2) identify patient-specific factors, including assessment of comorbid conditions, which may affect an individual's ability to tolerate treatment. Both disease- and patient-specific factors are taken into consideration when deciding treatment (NCCN 2019b).

Overview of clinical presentation

Common clinical manifestations of acute Leukemia result from clonal proliferation of myeloblasts (in AML) and lymphoblasts (in ALL), which replace normal bone marrow cells, leading to the inadequate production of erythrocytes (anemia), platelets (thrombocytopenia), and functionally normal white blood cells (WBC) (neutropenia) (**Table 1**).

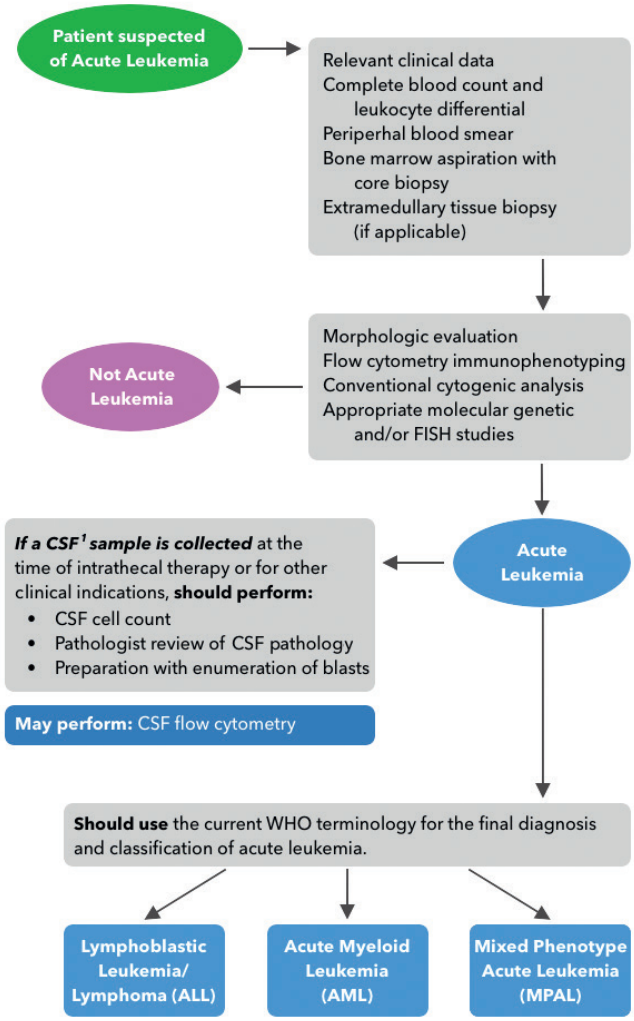

Figure 1: Initial diagnostic workup of acute Leukemia (Adapted from: Cessna 2017)

Table 1: Common Clinical Manifestations of Acute Leukemia at the Time of Patient Presentation

	Clinical Manifestation
Anemia	Fatigue Weakness Malaise Pallor Dyspnea on exertion
Thrombocytopenia	Mucosal bleeding Easy bruising Petechiae and purpura Spontaneous hemorrhage (intracranial, subdural, intraabdominal hematomas)
Neutropenia	Fever Susceptibility to infections

[1] CSF = Cerebrospinal fluid is a clear, colorless body fluid found in the brain and spinal cord. It is produced by specialised ependymal cells in the choroid plexuses of the ventricles of the brain, and absorbed in the arachnoid granulations.

The clinical presentation and site of leukemic involvement is often based on the type of leukemic blasts affected: leukostasis is more common in AML whereas lymphadenopathy is more commonly seen with ALL.

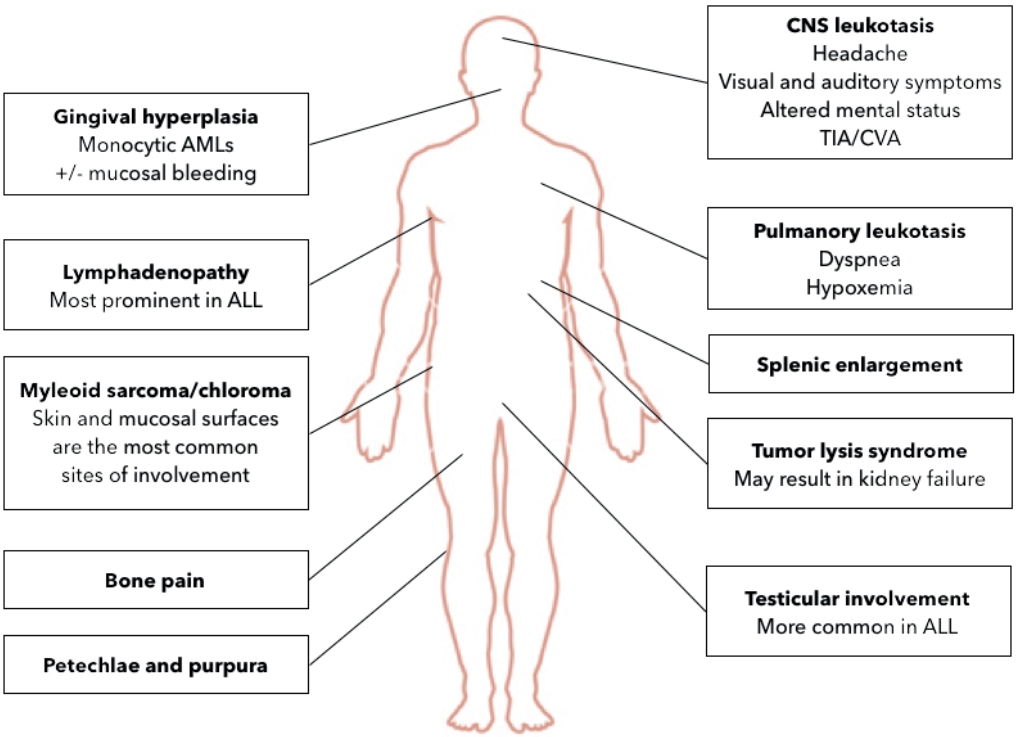

Figure 2. Anatomic site of potential leukemic involvement. ALL, acute lymphoblastic Leukemia; AML, acute myeloid Leukemia; CNS, central nervous system; TIA/CVA, transient ischemic attack/cerebrovascular accident. Adapted from: Duncan 2018.

Overview of common diagnostic practices

The diagnosis of acute Leukemia requires a comprehensive medical history and physical examination as well as morphologic assessment, determination of cytochemical and immune phenotypic features and evaluation of genetic abnormalities. The patient's performance status, using assessment tools such as the ECOG/WHO score, should be assessed as a general indication of ability to tolerate treatment.

To secure an accurate diagnosis, relevant clinical data, findings from physical examination and imaging tests should be performed and made available to the pathologist.

Table 2	
Clinical data of usefulness in establishing a diagnosis of acute Leukemia	Patient age, sex and ethnicity; history of any hematologic disorder or known predisposing conditions or syndromes; any prior malignancy; exposure to cytotoxic therapy, immunotherapy, radiotherapy or other possibly toxic substances; any additional clinical findings of diagnostic or prognostic importance
Data from physical examination and imaging tests of usefulness in establishing a diagnosis of acute Leukemia	Findings from neurologic examination; presence of tumor masses; other tissue lesions; presence of organomegaly including enlarged testicles
Source: Arber et al 2017	

Morphological assessment

Morphological and immunophenotypical evaluation of peripheral blood and bone marrow serve as the cornerstones for the diagnosis of acute Leukemia. Peripheral blood examination should be correlated with results of a complete blood count (CBC) including platelets and a differential of white blood cells (WBCs). Peripheral blood examination usually shows features of bone marrow failure, including anemia, thrombocytopenia and neutropenia. Blasts are usually present, but the number varies widely. Bone marrow core biopsy and aspirate analyses and cytogenetic and molecular analyses are necessary for risk stratification and to guide therapy decisions (NCCN 2019b).

A diagnosis of acute Leukemia generally requires at least 20% blasts in the peripheral blood or bone marrow. Cytochemical stains may be useful to identify blast lineages. Myeloid or lymphoid lineage is most frequently established by multiparameter flow cytometry (MFC). Together with cytomorphology and cytochemistry, flow cytometry immunophenotyping from a bone marrow aspirate is essential to define the lineage of the Leukemia cells and identify unusual phenotypic features that provide clues for specific types of acute Leukemia (Singh 2018). Specific immunophenotypic profiles have been associated with prognosis and/or unique cytogenetic and molecular abnormalities. Immunohistochemistry from a bone marrow aspirate is another diagnostic test used to identify morphology and may be useful when bone marrow aspirate is inadequate due to various reasons such as marrow fibrosis or packed marrow.

Cytogenetic analysis

Cytogenetic testing from bone marrow aspirate or peripheral blood is done to evaluate if chromosomes have any abnormalities such as translocation, inversion, deletion or addition/duplication of a chromosome. Because both AML and ALL are caused by a series of acquired genetic aberrations, the presence of genetic abnormalities should be evaluated using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics) and interphase fluorescence in situ hybridization (FISH) assays. Polymerase chain reaction (PCR) is a highly sensitive test used to detect gene and chromosome changes too small to be detected by karyotyping.

Table 3: Tests frequently performed to Diagnose Acute Leukemia

Test	Purpose
Cytochemistry	Cells from bone marrow specimen are stained to detect the type of proteins within cells
Immunophenotyping	Detects which cell type is present by analyzing proteins on the surface of cells; surface proteins are often targets for treatment. IHC: (immunohistochemistry): involves adding a chemical marker to cells obtained on biopsy; cells studied using a microscope Flow cytometry: Light-sensitive dye added to cells obtained from peripheral blood or bone marrow; cells are then passed through a machine that measures surface proteins on cells
Cytogenetics	Testing to detect defects in chromosomes; results help confirm and predict outcome of treatment Karyotype: standard method for chromosome analysis to detect chromosome abnormalities associated with malignancies; assess number of chromosomes (should be 23 pairs) and missing pieces of chromosomes FISH: special color dyes attach to DNA to assess for specific, pre-specified defects such as translocation or inversion of chromosomes
Molecular testing	Testing of genes or their products (proteins) to detect fusion genes made by translocations; results used to predict outcomes and plan treatment. Genes tested include FLT3, NPM1, CEBPA, IDH1, IDH2, TP53, KIT, ASXL1, RUNX1
PCR (polymerase chain reaction)	A molecular method used to analyze a short sequence of DNA to detect specific pre-specified mutations

Other assessment and workup practices

Because coagulopathy is common at presentation in many Leukemias, evaluation of prothrombin time, partial thromboplastin time and fibrinogen activity as part of the initial evaluation and before performing any invasive procedures is advisable.

Human leukocyte antigen (HLA) typing and an early evaluation and search for family or an alternative donor should be performed in all patients with newly diagnosed acute Leukemia for whom stem cell transplant would be considered [**Refer to Module 3 and 4 for more information on treatment options**].

In addition to CBC, other laboratory tests frequently performed during the workup of the patient with suspected acute Leukemia include: a comprehensive metabolic panel, serum uric acid and lactate dehydrogenase, liver function tests, a tumor lysis syndrome (TLS) panel, uric acid measurement, urine analysis and hepatitis B/C, HIV and cytomegalovirus (CMV) antibody evaluations. All patients should be evaluated for opportunistic infections as appropriate (NCCN 2019a; NCCN 2019b). Risk factors, such as existing cardiac disease or older age require further evaluation on an individual basis. If extramedullary disease, including central nervous system (CNS) disease, is suspected, a PET/CT or MRI is recommended. Patients with significant CNS signs or symptoms at presentation should be evaluated using appropriate diagnostic evaluation such as lumbar puncture or MRI.

Because of the relationship between level of fitness and treatment outcomes, evaluation should be performed to identify patients who may be unfit for intensive chemotherapy. These tests include evaluation of physical performance, comorbid conditions and cognitive function (Pettit 2015). Several prognostic models have been developed to risk –stratify and predict outcomes of patients undergoing induction chemotherapy based on patient and disease characteristics. Although older adults of the same chronologic age vary widely with respect to comorbidity, functional status, emotional health, cognitive performance, polypharmacy, social support and presence of geriatric syndromes, treatment decisions are often based on chronologic age only. There is currently no gold standard for assessment of fitness, unfitness or frailty. In older patients, a geriatric assessment may prove helpful to evaluate individual patient characteristics in a standardized fashion (Klepin 2019) to better plan individualized treatment.

Patients and their partners should receive fertility counseling and preservation options should be discussed with all patients.

Measurable Residual Disease

Measurable residual disease (MRD; previously termed minimal residual disease) refers to submicroscopic disease. MRD can help predict the effectiveness of a treatment and identify patients at higher risk for relapse, allowing for earlier or additional treatments. Increasing evidence suggests that the ability to identify residual disease far below the morphology-based 5% blast threshold is important to define risk classification (Schuurhuis 2018).

There are several methods used to evaluate MRD, including multiparameter flow cytometry (MFC), real-time quantitative polymerase chain reaction (RQ-PCR), next generation sequencing (NGS) and digital PCR. The detection of MRD significantly correlates with the clinical outcome in acute Leukemia. Testing for MRD can be done at different time points in the course of managing acute Leukemia based on disease-specific factors.

Diagnosis of Acute Myeloid Leukemia (AML)

Clinical presentation and physical findings

The most common laboratory findings at the time of diagnosis in patients suspected of having AML are listed in **Table 4**.

Diagnostic workup for AML

The initial diagnostic workup for patients suspected of having AML consists of a comprehensive medical history and physical examination (**Fig. 3**). The specific laboratory tests and procedures commonly used in the diagnostic workup are explained in the section "Overview of Common Diagnostic Practices" above.

In accordance with the 2016 WHO classification, a diagnosis of AML is made based on the presence of ≥- 20% blasts in the marrow or peripheral blood. However, a diagnosis of AML may be made with < 20% blasts in patients with recurrent cytogenetic abnormalities including t(15;17), t(8;21), t(16;16) or inv(16), thus emphasizing the importance of the identification of specific recurrent genetic abnormalities in diagnosing AML (Arber 2016; Döhner 2017). The results of the diagnostic workup assist in defining risk stratification and guiding therapy.

Table 4: Common Laboratory Findings at Diagnosis of AML

Feature	AML
Platelets	Low in > 90%
Anemia	Severe in > 90%
WBC count	High in 60% Normal or low in 40%
Differential WBC count	Many myeloblasts
Lymphadenopathy	Occasionally present
Splenomegaly	In 50%
Other features	CNS rarely involved

Source: Arber et al 2017

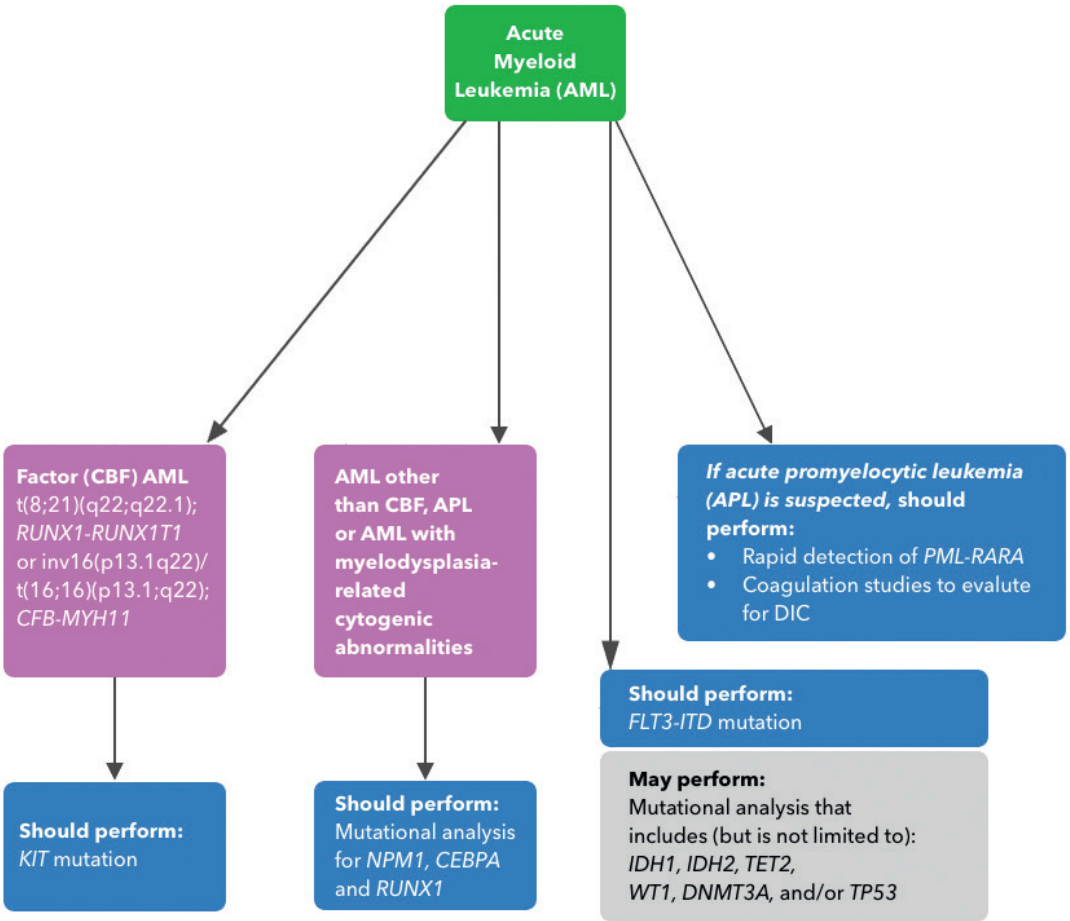

Figure 3. Initial diagnostic workup of acute myeloid Leukemia

Laboratory tests frequently performed to diagnose and subsequently classify AML include:

- Complete blood count including platelets and a differential of WBCs as well as prothrombin time, partial thromboplastin time and fibrinogen activity
- Serum uric acid and lactate dehydrogenase
- Bone marrow core biopsy and aspirate analyses (including immunophenotyping and cytochemistry)
- Cytogenetic analyses of bone marrow (karyotype, possibly fluorescence in situ hybridization [FISH])
- Testing for gene mutations in c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1 and TP53

Although peripheral blood involvement is frequent, infiltration of organs, most frequently the brain and/or lung, is rare in AML and seen most often in patients with high blood blast counts (eg, > 50,000/µL) (Estey 2018).

Classification schema for AML

The classification and understanding of AML has progressed from purely focusing on morphological features, cytogenetics, and phenotypic characteristics to a greater emphasis on molecular genetic abnormalities. The World Health Organization (WHO) classification defines AML in terms of disease entities categorized by cytogenetic and molecular genetic subgroups. It is important to note that detection of these genetic abnormalities such as chromosomal rearrangements and/or gene mutations is crucial in AML and these distinct entities carry different prognoses and therapeutic implications. In recent years, there have been many important breakthroughs in understanding the genomic landscape of AML. There has also been rapid progress in identifying different types of mutations and understanding their clinical significance, and in many instances, developing specific therapies directed at such abnormalities. The 2017 European LeukemiaNet (ELN) guidelines for Diagnosis and Management of AML in adults recommend screening patients to identify mutations at diagnosis (Döhner 2017). Molecular testing of these abnormalities is not only of prognostic value, but can aid a more individualized approach to patient management.

The World Health Organization (WHO) proposed a classification system for acute Leukemia based on the premise that clinically meaningful classification uses a combination of morphology, cytochemistry, immunophenotype, genetics and clinical features to define clinically significant disease entities. According to the WHO classification system, AML can be broadly divided into three major groups: a genetically defined group (AML with recurrent genetic abnormalities), a biologically defined group (AML with MDS-related changes or AML secondary to previous therapy) and a group based on cell morphology and lineage origin (AML, AML not otherwise specified) (**Fig. 4**).

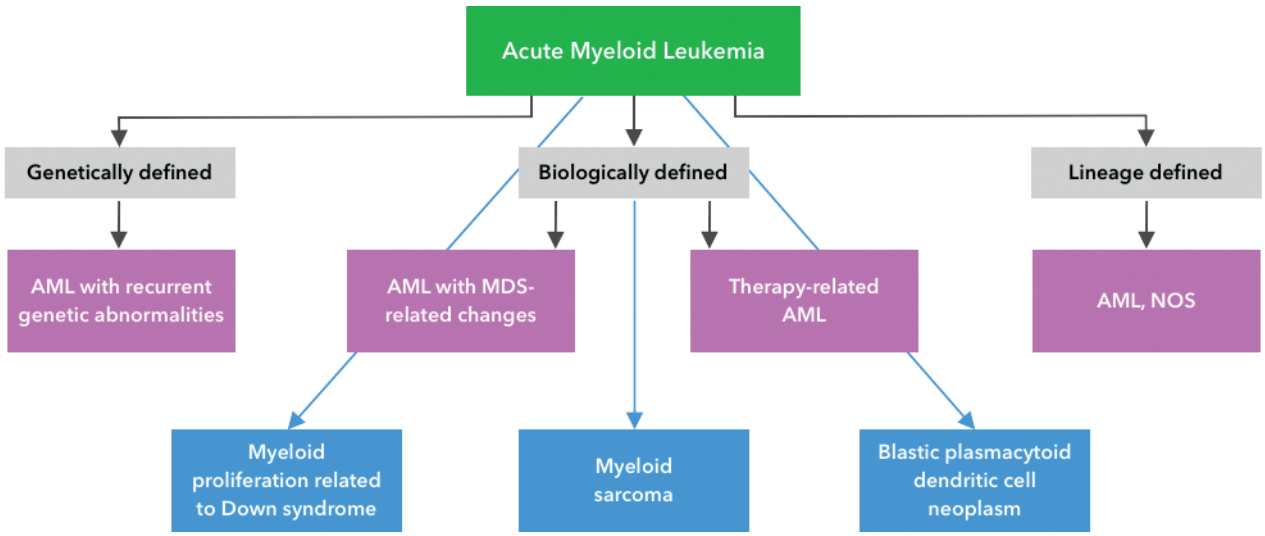

Figure 4: Major categories of AML based on the WHO 2008 classification (Adapted from: Singh 2018) AML, acute myeloid Leukemia; MDS myelodysplastic syndrome; NOS, not otherwise specified

In 2016, WHO expanded the classification of recurrent genetic abnormalities, which now identifies seven subtypes of AML with recurrent cytogenetic abnormalities (**Fig. 5**).

AML with t(8;21)(q22;q22), (AML1/ETO); AML with abnormal bone marrow eosinophils and inv(16)(p13q22) or t(16;16)(p13)(q22), (CBFB/MYH11);
APL with PML/RARa;
AML with t(9;11)(p21.3;q23.3), (MLLT3-KMT2A);
AML with t(6;9)(p23;q34.1), (DEK-NUP214);
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2), (GATA2, MECOM);
AML (megakaryoblastic) with t(1;22)(p13.3q133), (RBM15-MKL1), AML with BCR-ABL1;
AML with mutated NPM1;
AML with biallelic mutations of CEBPA. AML with mutated RUNX1

Figure 5: AML with Recurrent Genetic Abnormalities (Arber 2016)

With a frequency of approximately 30%, AML with NPM1 mutation represents the largest group of genetic abnormalities (Bullinger 2017). Genomic aberrations underlying AML in elderly patients have been less well characterized and there seems to be a shift toward more unfavorable genomic groups with increasing age (Bullinger 2017).

Prognostic factors and risk stratification in AML

An accurate assessment of prognosis is key to the management of acute Leukemia. Stratification of risk will allow the determination of the most appropriate treatment, including making a decision about stem cell transplantation. Certain patient- and cytogenetic variables can affect prognosis.

The presence of co-morbidities and several host factors can adversely affect treatment outcomes. For example, patients aged ≥ 60 to 65 years are more susceptible to treatment complications (particularly severe infections) than younger patients, which contributes to a higher risk of an unfavorable outcome. Pre-existing medical conditions such as diabetes, coronary heart disease or chronic pulmonary obstructive disease can contribute to poor risk. Other risk factors with a potential to affect prognosis include:

- History of smoking, previous chemotherapy treatment, radiation exposure
- Auto-immune disorders (i.e., rheumatoid arthritis, auto immune hemolytic anemia, ulcerative colitis)
- Complex karyotype abnormalities (> 3)
- Monosomal karyotype (Fey 2013)

Although cytogenetic information is often unknown when treatment is initiated in patients with de novo AML, karyotype represents the single most important prognostic factor for predicting remission rates, relapse risks and overall survival (OS) outcomes (NCCN 2019b). Therefore, full karyotyping and FISH cytogenetic analysis are important diagnostic procedures in AML. Based on retrospective analysis of larger studies, 40% to 50% of patients with de novo AML have normal karyotype, which is associated with intermediate risk as measured in terms of survival outcomes.

The European LeukemiaNet (ELN) established a 3-group genetic risk classification system for AML (Döhner 2017). This stratification categorizes risk based on genetic categories as "favorable", "intermediate" and "adverse". The stratification was originally developed to standardize reporting of genetic abnormalities and to correlate those with clinical characteristics and outcomes in AML to standardize risk assessment.

While genomic lesions heavily contribute to predictions of event-free survival and OS in AML, models used to predict if a patient will enter remission or life expectancy are correct in only 75% to 80% of cases (Döhner 2017). Further, the prognostic impact of many gene markers is context-dependent: the effect of a given abnormality depends on the presence or absence of another (Döhner 2017).

Acute Promyelocytic Leukemia (APL)

APL is a particularly aggressive subtype of AML and comprises approximately 10% of AML cases (NCCN 2019b). APL has a distinct morphology and clinical presentation that may be associated with a high early mortality due to potentially fatal coagulopathy. Whereas AML commonly occurs in patients older than 65 years, APL tends to occur at a younger age. APL can be de novo or therapy-related (NCCN 2019b). Some of the reported attributes of APL are: average age at diagnosis is 47 years with a higher incidence in women; the single mutation t(15;17) is most common; remission rate is approximately 80 - 98% (Platzbaker 2017, Rashidi 2013).

Diagnostic Workup of Acute Lymphoblastic Leukemia (ALL)

Clinical presentation and physical findings in ALL

The clinical presentation of ALL is typically nonspecific, and may include fatigue or lethargy, constitutional symptoms (e.g., fevers, night sweats, weight loss), dyspnea, dizziness, infections and easy bruising or bleeding. The most common laboratory findings at the time of diagnosis in patients suspected of having ALL are listed in **Table 5**.

Table 5: Common Laboratory Findings at Diagnosis of Acute Lymphoblastic Leukemia

Feature	ALL
Platelets	Low in > 80%
Anemia	Severe in > 90%
WBC count	High in 50% Normal or low in 50%
Differential WBC count	Many lymphoblasts
Lymphadenopathy	Commonly present
Splenomegaly	In 60%
Other features	Without prophylaxis, CNS commonly involved

WBC, white blood cell; CNS, central nervous system
Source: Arber et al 2017

Diagnostic workup for ALL

The initial diagnostic workup for patients suspected of having ALL consists of a comprehensive medical history and physical examination (**Fig. 6**). The specific laboratory tests and procedures commonly used in the diagnostic workup are explained in the section "Overview of Common Diagnostic Practices" above.

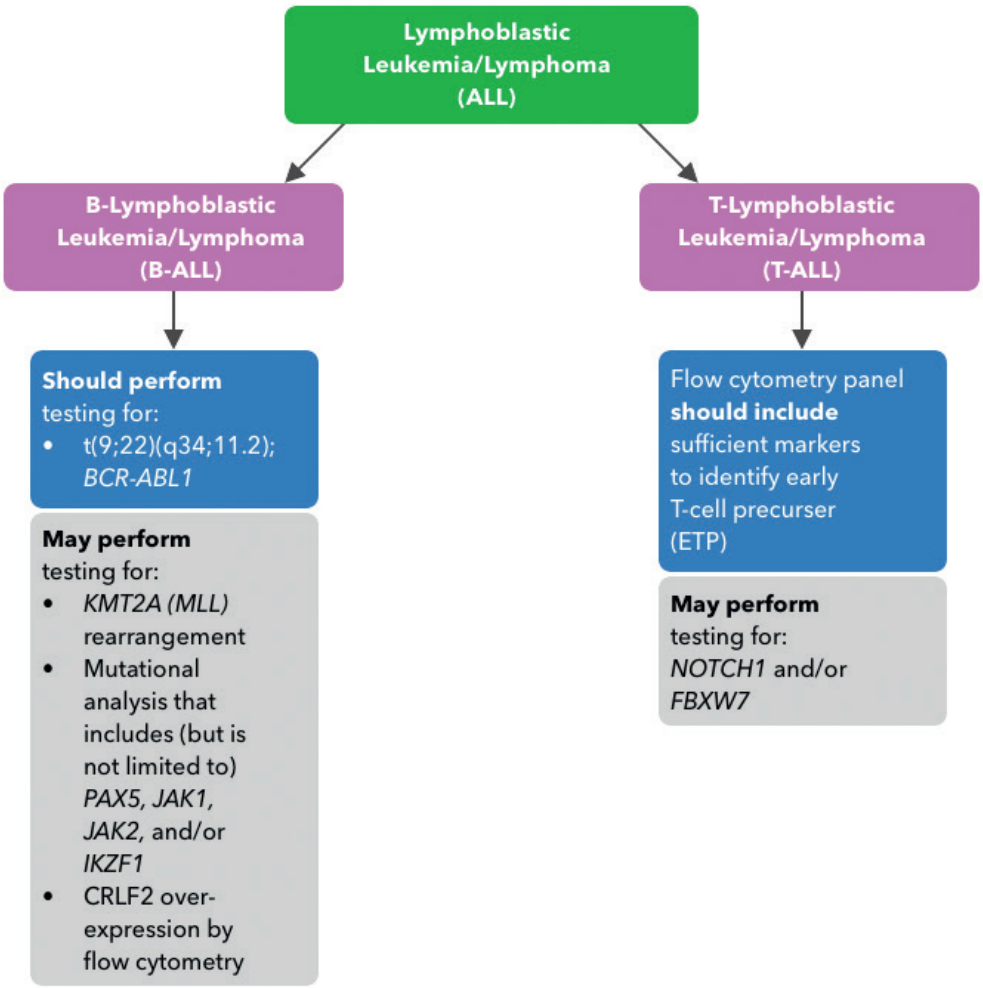

Figure 6. Initial diagnostic workup of acute lymphoblastic Leukemia (Cessna 2017)

The diagnosis of ALL generally requires demonstration of ≥ 20% bone marrow lymphoblasts on review of bone marrow aspirate and biopsy materials (NCCN 2019a). The performance of morphologic, immunophenotypic and molecular diagnostic procedures in ALL serves to:

- Confirm ALL diagnosis
- Distinguish B-cell precursor ALL from T-cell ALL
- Distinguish Burkitt Leukemia from B-cell precursor ALL
- Distinguish Philadelphia (Ph) chromosome-positive (Ph+) ALL from Ph-negative (Ph-) ALL
- Shorten time to treatment start

In addition to the initial workup procedures recommended for acute Leukemia, patients suspected of having ALL should also undergo liver and renal function tests, a disseminated intravascular coagulation panel and a tumor lysis syndrome panel, urinalysis and hepatitis B/C, HIV and cytomegalovirus (CMV) antibody evaluations. Appropriate imaging studies (e.g., CT/MRI scan of the head with contrast) should be considered to detect meningeal disease, chloromas or central nervous system bleeding for patients with neurologic signs or symptoms at diagnosis. A thorough evaluation for evidence of active infection should be conducted. Female patients should undergo pregnancy testing and all male patients should be evaluated for testicular involvement of disease, including a scrotal ultrasound as indicted (testicular involvement is common in cases of T-cell ALL). Further, because many treatment protocols include the use of an anthracycline, an echocardiogram or cardiac scan should be considered at the time of initial diagnostic workup.

Classification schema for ALL

ALL can present as Leukemia when neoplastic cells (lymphoblasts) involve blood and bone marrow (≥ 25% bone marrow blasts), or as lymphoma when blasts mainly infiltrate extramedullary tissue. There are many types of ALL, differentiated based on characteristics of the lymphoblasts. The European LeukemiaNet has developed a classification of ALL based on the immunophenotype of the lymphoblasts when analyzed by flow cytometry. Approximately 75% of ALL in adults is subtypes of B-cell lineage, the remaining 25% comprise T-cell lineage ALL.

Type and Subtype	Frequency in Adults
B-cell ALL	
• Pro-B or pre-pre B	20%
• Common	40%
• Pre-B	10%
• Mature B	5%
T-cell ALL	25%
• Pro-T	
• Pre-T	
• Cortical thymic	

Source: European LeukemiaNet. Available at: https://www.Leukemia-net.org/content/patients/Leukemias/all/e4417/infoboxContent4418/ALL.pdf. Accessed July 2019

Therefore, ALL can be divided into two main groups and two subgroups. The two main groups are:

B-cell ALL (B-ALL): characterized by the presence of characteristic markers of normal B lymphocytes on the surface of the cells

T-cell ALL (T-ALL): characterized by the presence of characteristic markers of T lymphocytes on the surface of the cells.

These two subgroups of ALL are clearly differentiated from other types by their characteristics; treatment of these forms of ALL is very different from the other types.

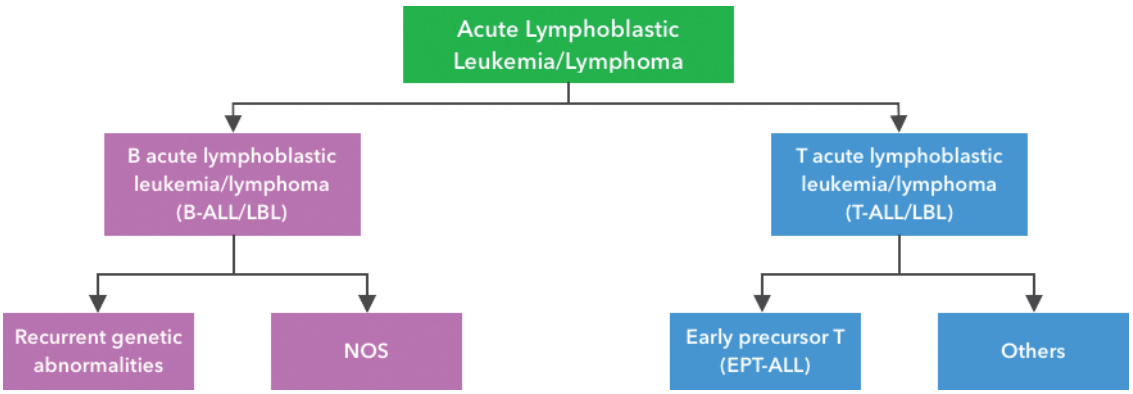

Figure 7. Overview of classification of acute lymphoblastic Leukemia (Adapted from: Singh 2018) EPT-ALL, early precursor T-cell acute lymphoblastic Leukemia; LBL, lymphoblastic lymphoma; NOS, not otherwise specified

ALL with Philadelphia chromosome (Ph+ ALL): a type of ALL in which there is an interchange of genes between chromosomes 9 and 22 (**Fig. 8**). This is the most common alteration or translocation in chromosomes in ALL and leads to the production of abnormal proteins, which are involved in the development of Ph-ALL. Ph-ALL is more frequent in older adults; response to conventional chemotherapy is poor although newer treatments have improved prognosis (see **Module 4**).

Burkitt's ALL: a type of ALL in which there is an alteration between chromosomes 8 and 14. Also referred to as mature B-ALL, this subtype has an incidence of < 5% of all ALL cases. Mature B-ALL has shown a good response to chemotherapy.

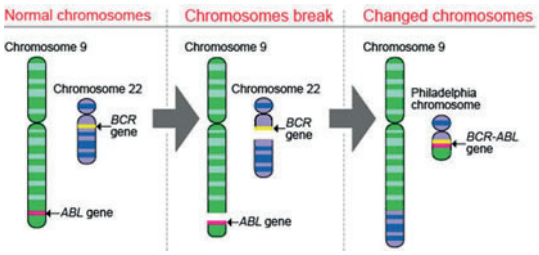

Figure 8. Philadelphia chromosome. The Philadelphia chromosome is formed by a translocation between parts of chromosomes 9 and 22 and contains the abnormal BCR-ABL1 fusion gene.

Prognostic factors and risk stratification in ALL

Various disease-related and patient-specific factors may have prognostic significance in patients with ALL. Although older age, a higher initial white blood cell count and CNS involvement are considered clinically significant prognostic factors (NCCN 2019a; Terwilliger 2017), the presence of the Philadelphia chromosome, t(9;22), is the most significant risk factor.

- Age: patients over the age of 60 have particularly poor outcomes
- Presence of metastasis to the brain or spinal cord
- Presence of changes in the genes, including the Philadelphia chromosome (Ph+ ALL), a translocation between chromosomes 4 and 11, a translocation involving chromosome 14, amplification of part of chromosome 21, < 44 chromosomes (hypodiploidy), ≥ 5 chromosome changes (complex karyotype)
- Elevated WBC at diagnosis (> 30 x 10^9 for B-ALL or >100 x 10^9 for T-ALL)
- Previous treatment or disease recurrence
- MRD+ after anti-leukemia therapy, especially in previously untreated patients.

While the diagnostic work-up identifies some high-risk subsets, the individual prognosis, however, is highly refined by ALL response dynamics. For example, patients presenting with no risk factors are defined as standard risk. Older age, reduced tolerability to treatments and higher WBC on presentation are universally recognized as independent risk variables predicting lower complete remission rate and shorter complete remission duration (Hoelzer 2016). The kinetics of response to early treatment is also well recognized and increasingly used for prognostic information.

The importance of risk stratification to identify appropriate treatment and help predict treatment response highlights the need for a rapid yet comprehensive diagnostic approach in ALL.

The cure rates and survival outcomes in ALL have improved over the past several decades, largely owed to incorporation of pediatric treatment protocols in the adult population, advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of risk-adapted therapy, the advent of new targeted agents and the use of allogeneic hematopoietic cell transplantation. The current five-year relative survival is 35% for ALL (American Cancer Society, 2019). In view of the poor prognosis associated with Ph+ ALL and the wide availability of agents that specifically target the BCR-ABL kinase, initial risk stratification for all patients is based on the presence or absence of the t(9;22) chromosomal translocation and/or BCR-ABL fusion protein.

ALL in Adolescents and Young Adults (AYA)

In ALL, adult patients are defined as those age ≥ 40 years; adolescent and young adults (AYA) are typically defined as those age 15 to 39 years. Overall 5-year survival (OS) of AYA with ALL have improved. SEER database data, for example, show an OS of 61% in this population. Cure rates for the AYA population remain lower than those for children, although substantial improvements have been seen with the recent adoption of pediatric treatment regimens. In this respect, AYA patients represent a unique population because they may receive treatment based on either a pediatric or an adult protocol, depending on local practices. Data suggest that AYA patients aged 15 to 21 years treated using a pediatric protocol have substantially improved event-free survival (EFS) compared to same-age patients treated on adult ALL protocols. However, compared to children, AYA patients have a lower frequency of favorable chromosomal/cytogenetic abnormalities, such as hyperdiploidy or ETV6-RUNX1, and

a greater incidence of poor-risk cytogenetics including Ph-positive ALL, hypodiploidy and complex karyotype, and a higher incidence of ETP-ALL (NCCN 2019a).

Future Perspectives in Acute Leukemia

Genomics-based knowledge data banks and outcome prediction models will become valuable tools to identify disease-relevant genes. Using novel genetic information to inform clinical practice is an active field of research. Given the enormous genomic heterogeneity of the disease, studies of several thousand patients will likely be needed to capture the clinical significance of the complex genetic architecture and to delineate how mutational profiling can be used to guide clinical decision-making. While novel targeted therapeutic approaches hold promise for improving patient outcomes, it is important that genomics-based outcome prediction systems remain flexible and adaptable to reflect these treatment advances and changes in disease monitoring (Bullinger 2017).

The field of technological possibilities to measure MRD more accurately is also rapidly expanding, and has begun to offer the possibility of capturing Leukemia heterogeneity at the single-cell level.

Advances in medicine, pharmacogenomics and technology will make it possible to optimize treatment by focusing on genetic makeup and tumor growth to personalize treatment options.

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Quick Facts

- Better knowledge of the pre-treatment mutation status of various genes has allowed for targeted treatment in some patients; treatment has now become highly individualized
- Physiologic measures, rather than chronologic age, are likely better predictors of tolerance of chemotherapy
- Standard induction therapy is known as 7 + 3 and is an anthracycline- and cytarabine-based regimen; the goal of therapy is to eliminate all detectable Leukemia cells and restore normal hematopoiesis
- Acute myeloid Leukemia affects predominantly older adults and, although the general prognosis is relatively poor for this population, the majority of patients benefit from treatment
- The major reason patients are not cured is resistance to treatment, often manifested as relapse from remission, rather than treatment-related mortality, whose incidence is decreasing
- Acute promyelocytic Leukemia can be life-threatening; even before a diagnosis is established, therapy with all-trans retinoic acid (ATRA) and measures to counteract coagulopathy should be initiated

Module III: Treatment of Acute Myeloid Leukemia

A. Introduction[1]

1. Overview of treatment strategies
2. Consideration of patient-related factors when deciding treatment
3. Consideration of disease-related factors when deciding treatment

B. Induction Therapy

C. Intensive Post-remission Therapy

1. Conventional intensive consolidation
2. Intensive chemotherapy followed by autologous hematopoietic stem cell transplantation
3. Conditioning followed by allogeneic stem cell transplantation
   a. Myeloablative conditioning versus reduced intensity conditioning
4. Measureable residual disease

D. Treatment of Relapsed Disease and Primary Refractory Disease

E. Treatment Strategies for Medically Fit Elderly Patients

F. Treatment Strategies for Medically Unfit Elderly Patients

G. Novel Approaches to Treating AML: Immunotherapy

H. Treatment Strategies for Acute Promyelocytic Leukemia

1. Management of coagulopathy
2. Management of hyperleukocytosis
3. Initial treatment of acute promyelocytic Leukemia

I. Treatment for Therapy-related Acute Myeloid Leukemia

J. Supportive Care

K. Management of Early Crisis

1. Tumor lysis syndrome
2. Hyperleukocytosis, leukostasis
3. Febrile neutropenia

L. Nursing Implications of Agents Commonly used in AML

References

Appendix 1: Response Criteria in AML

Appendix 2: Steps involved in Allogeneic Hematopoietic Cell Transplantation (HSCT)

Resources

[1] Because new agents are continually being developed and evaluated for use in AML, treatment options change quickly. The information contained in this module will be regularly updated to reflect these developments.

Introduction: Treatment Strategies in Acute Myeloid Leukemia

The general treatment strategy for acute myeloid Leukemia (AML) has not changed substantially in over 40 years. That is, the therapy is based on an initial assessment of overall medical fitness to determine whether a patient is a suitable candidate for intensive chemotherapy (Stone 2019). It is recommended to treat patients with AML in centers experienced in the comprehensive management of these patients in a setting in which a multidisciplinary infrastructure is in place (Fey 2013). Whenever possible, treatment should be as intensive as possible (allowing for individual patient tolerance) and designed to provide a cure of AML. There are 2 phases of treatment: induction and intensive post-remission therapy. While all patients should receive supportive care, less intensive treatment focused on alleviation of symptoms may be an appropriate treatment option for some patients.

Both disease- and patient-related factors are taken into consideration during the treatment decision process. Because of the intensity of treatment and the myelosuppressive side effects of chemotherapy agents used to treat AML, patients should be evaluated for the presence of active infection before treatment initiation. This evaluation generally includes a careful clinical exam as well as additional techniques to identify the presence of infection such as computed tomographic scans of the chest and abdomen and radiological imaging of teeth and jaws to identify dental root granulomas and caries. Preparation for intensive treatment also often includes insertion of a central venous catheter. The collaboration of a multidisciplinary team is essential to ensuring not only optimal clinical outcomes, but optimal quality of life for the patient with AML.

Consideration of patient-related factors

The various patient-related risk factors with a potential to affect treatment decisions are discussed in **Module 2** [see Prognostic factors and risk stratification in AML]. Age 60-65 years represents a therapeutic divergence point for both NCCN and ELN treatment recommendations. Now, more importantly than chronologic age, the presence of co-morbidities, patient wishes and availability of social support systems should be taken into consideration when planning treatment. Other factors to assess when considering treatment options include:

- Cognitive function
- Polypharmacy
- Functional status
- Nutrition status
- Mental health/presence of depression

Medical fitness for tolerating intensive chemotherapy can be estimated relatively accurately with multiparameter assessment tools; this information should serve as basis for the assignment to intensive or less intensive therapy. Determination of fitness for intensive therapy should not be based on a single factor (such as age) but a combination of factors to optimize predictive accuracy (Walter 2015). In older patients especially, the use of comprehensive, validated geriatric assessment tools that focus on cognitive and physical function can help predict treatment tolerability and improve the prediction of survival (Klepin 2013).

The prognosis in patients diagnosed at about age 65 years is more dismal than that of younger patients. Older age is often accompanied by frailty, a low functional reserve and comorbidities, which negatively affect the tolerance of intensive treatment modalities.

The prompt initiation of specific treatment for AML is essential to improve life expectancy. Despite this situation, only 40% of elderly patients receive specific AML therapy within the first 3 months from diagnosis in the US according to SEER-Medicare data (Medeiros 2015). Still, a favorable outcome is dependent on the administration of an effective treatment and the risk versus benefit of subjecting a patient to intensive chemotherapy must be evaluated based not only on the predicted toxicity of the regimen, but also on the likelihood of response (Almeida 2016). In this light, there is evidence to support the fact that patients treated with low-intensity regimens live longer than those who receive supportive measures only (Dombret 2015; Kantarjian 2012).

Consideration of disease-related factors

Molecular and genetic risk factors with a potential to affect treatment decisions are discussed in **Module 2** [see Prognostic factors and risk stratification in AML]. Genetic abnormalities are powerful prognostic factors in AML. RUNX1 mutations identify patients with poor prognosis. Similarly, ASXL1 mutations are also associated with inferior survival. The prognostic impact of many markers is context-dependent with the effect of a given abnormality dependent on the presence or absence of another. For example, a NPM1 mutation conveys a "favorable" prognosis only in the absence of a FLT3-ITD, whereas mutations in both ASXL1 and RUNX1 confer a particularly poor prognosis. (Döhner 2017).

Induction Therapy

The backbone of induction therapy is an anthracycline (daunorubicin or idarubicin) and cytarabine (cytosine arabinoside, Ara-C) based regimen, which is associated with severe bone marrow and gastrointestinal toxicities. This standard induction therapy is known as 7 + 3 and the

goal of therapy is to eliminate all detectable Leukemia cells and restore normal hematopoiesis (**Table 1**). The induction stage of treatment is not always successful and may need to be repeated before intensive post-remission therapy can begin. It is important that patients complete induction in a condition that allows them to tolerate more intensive treatments during consolidation to achieve durable disease control: without post-remission therapy, relapse usually occurs within 6 to 9 months (NCCN 2019). Although cytogenetic and molecular abnormalities are the most significant prognostic indicators, failure to achieve remission after 1 cycle of induction therapy or high tumor burden, defined as a white blood count (WBC) ≥ 40,000/mcL, are poor-risk factors for long-term remission (NCCN 2019).

Table 1: Selected Conventional Therapy Regimens for AML

Patients eligible for intensive chemotherapy	
Induction therapy *, †, ‡	
all ages (7 + 3)	3 d of an IV anthracycline: daunorubicin at least 60 mg/m^2; idarubicin 12 mg/m^2; or mitoxantrone 12 mg/m^2, and 7 d of continuous infusion cytarabine (100-200 mg/m^2)
Consolidation therapy ‡, §	
Younger patients (18-60/65 y) Favorable-risk genetics Intermediate-risk genetics Adverse-risk genetics	 2-4 cycles of IDAC (1000-1500 mg/m^2 IV; or 1000-1500 mg/m^2 IV Allogeneic HSCT 2-4 cycles of IDAC (1000-1500 mg/m^2 IV; or 1000-1500 mg/m^2 IV, or High-dose therapy and autologous HSCT Allogeneic HSCT
Older patients (> 60/65 y) Favorable-risk genetics Intermediate-risk genetics	 2-3 cycles of IDAC (500-1000 mg/m^2 IV; or 500-1000 mg/m^2 IV No established value of intensive consolidation therapy; consider allogeneic HSCT in fit patients, or investigational therapy
Patients not eligible for intensive chemotherapy	
Azacitidine ¶	75 mg/m^2, SC, q4 wk, until progression
Decitabine #	20 mg/m^2, IV, q4 wk, until progression
Low-dose cytarabine **	Low-dose cytarabine (20 mg SC, q4 wk; until progression); not recommended in patients with adverse-risk genetics
Best supportive care Venetoclax + HMA (Azacitidine or decitabine) Venetoclax + LD-AraC	Hydroxyurea; for patients who cannot tolerate any anti-leukemic therapy, or who do not wish any therapy
Salvage regimens in patients not responding to first induction or with relapsed disease and candidates for intensive therapy	
IDAC †† (with or without anthracycline)	IDAC (1000-1500 mg/m^2 IV [500-1000 mg/m^2 in patients >60 y]; or 1000-1500 mg/m^2 IV [500-1000 mg/m^2 in patients >60 y]); with or without daunorubicin 45-60 mg/m^2, IV; idarubicin 8-10 mg/m^2, IV, or mitoxantrone 8-10 mg/m^2, IV
FLAG-IDA ‡‡	Fludarabine 30 mg/m^2 IV; cytarabine 1500-2000 mg/m^2 IV starting 4 h after fludarabine infusion; idarubicin 10 mg/m^2 IV; G-CSF 5 mg/kg, SC; additional G-CSF may be administered starting 7 d after end of chemotherapy until WBC count >500/uL Consider dose reduction in patients >60 y: fludarabine 20 mg/m^2; cytarabine 500-1000 mg/m^2; idarubicin 8 mg/m^2

Table 1: Selected Conventional Therapy Regimens for AML	
MEC	Mitoxantrone 8 mg/m^2; etoposide 100 mg/m^2; cytarabine 1000 mg/m^2
Allogeneic HSCT	Consider transplantation for patients with primary refractory disease, for patients in second CR or with major cytoreduction but still active disease following salvage therapy Consider second transplantation under certain conditions (see "Salvage treatment") Perform early HLA typing

FLAG, FLudarabine, Arabinofuranosyl cytidine, GCSF; FLAG-AMSA, FLAG + amsacrine; FLAG-MITO, FLAG + mitoxantrone; q, every; HSCT, hematopoietic cell transplantation; IDAC, intermediate dose ARA-C; SC, subcutaneously; y, year
*Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of 7 + 3 (see common salvage regimens)
† Older patients (generally >65 y) and patients with adverse genetics are less likely to respond to conventional induction therapy and may receive hypomethylating agents or investigational therapy
‡ Patients, at least those aged 18 to 60 y, with newly diagnosed AML and activating FLT3 mutations may be considered to receive additional therapy with midostaurin (after chemotherapy)
§ Results from assessment of MRD should be taken into account for selecting the appropriate consolidation therapy
¶ Approved by FDA and EMA for patients not eligible for HSCT with 20% to 30% blasts and multilineage dysplasia; in addition, approved by EMA for patients not eligible for allogeneic HSCT with > 30% marrow blasts
# Approved by EMA for patients with newly diagnosed de novo or secondary AML, who are not candidates for standard induction chemotherapy
** 20 mg/m^2 SC used in some countries
†† Evidence from clinical trials indicate that doses > 1500 mg/m^2 are above the plateau of the maximal therapeutic effect; single-agent IDAC should not be used in patients relapsing within 6 mo following consolidation with higher doses of cytarabine
‡‡ Idarubicin may be replaced by mitoxantrone 10 mg/m^2 IV (FLAG-MITO); or by amsacrine 100 mg/m^2 (FLAG-AMSA)
Adapted from: Döhner 2017

Intensive Post-remission Therapy

Post-remission therapy is warranted once a patient has reached clinical and hematological remission (**see Appendix 1**). The aim of this therapy phase is to clear any remaining, undetected Leukemia cells and prevent relapse. This treatment phase involves intensive and high-dose chemotherapy followed by autologous or allogeneic HSCT (**Fig. 1**). The post-remission phase of treatment often lasts several months. Currently, maintenance chemotherapy is not part of standard AML treatment due to a lack of convincing evidence of benefit.

Conventional intensive consolidation

Consolidation regimens usually include single-agent cytarabine at high doses with or without multiagent chemotherapy. Most commonly, up to 4 cycles of high-dose cytarabine (2000 to 3000 mg/m^2) are administered, although there is no convincing evidence that high doses are more effective than intermediate doses (1000 to 1500 mg/m^2) (Döhner 2017). Practice differs in the number of cycles of post-remission treatment required.

Intensive chemotherapy followed by autologous hematopoietic cell transplantation

One cycle of intensive chemotherapy (myeloablative) followed by autologous HSCT using peripheral blood CD34+ cells offers condensed treatment (Döhner 2017). According to retrospective analyses, autologous HSCT leads to better event-free survival and relapse-free survival than chemotherapy, an effect that is mainly apparent in favorable- and intermediate-risk disease (Döhner 2017).

Conditioning followed by allogeneic hematopoietic cell transplantation

Allo HSCT from a matched sibling or an unrelated donor is commonly performed in AML in first remission. The use of mismatched donors as well as cord blood and haplo options now allows a wider opportunity for finding a donor for most patients. The decision to perform allogeneic HSCT (allo-HSCT) is based on the risk versus benefit ratio (non-relapse mortality/morbidity versus reduction of relapse risk), which is based on cytogenetic and molecular genetic features as well as patient, donor and transplant factors. Generally, allo-HSCT is recommended when the relapse

incidence without transplant is expected to be > 35% to 40% (Döhner 2017). Monitoring of measureable residual disease (MRD; sometimes referred to as minimal residual disease) serves as a guide for treatment decisions (**see Appendix 2**).

Myeloablative conditioning versus reduced intensity conditioning

Myeloablative conditioning regimens do not allow for autologous recovery and require stem cell support. A reduced intensity conditioning may be more appropriate for older age patients or for patients with significant comorbidities. This treatment option relies on a graft-versus-Leukemia effect, mediated by infused donor T cells, rather than the cytoreductive effect of myeloablative conditioning (Wall 2017). The availability of non-myeloablative or reduced-intensity conditioning regimens mean that older patients, in some cases up to age 75, can be transplanted while the dose of total body irradiation or the alkylating agent is usually reduced by at least 30% compared with an ablative regimen (Cornelissen 2016). Two commonly used regimens for reduced intensity conditioning are busulfan/fludarabine and fludarabine/low-dose total-body irradiation. The former is more intensive or more myeloablative and often used in younger patients, healthy patients and the latter in elderly patients or those with severe comorbidities. Myeloablative conditioning regimens often combine cyclophosphamide with total body irradiation or a busulfan plus cyclophosphamide regimen.

Partial or complete T-cell depletion and post-transplant cyclophosphamide may reduce the risks of acute and chronic graft-versus-host disease (GVHD). The biggest challenge, however, remains the prevention of post-transplant relapse for which various treatments are being tested.

Measureable residual disease

Complete remission, as defined by conventional morphological criteria, is a highly heterogeneous state with a wide range of residual Leukemia burden. In this light, many patients in complete remission actually have residual disease that will lead to clinically evident relapse if additional treatment is not administered. Therefore, evaluation of MRD will often be performed:

1) At early time points such as following induction and consolidation therapies to assess remission status and determine kinetics of disease response

2) Sequentially beyond consolidation to detect impending morphologic relapse (Döhner 2017).

[**See Module 2 for more information on MRD**].

Treatment of Relapsed Disease and Primary Refractory Disease

The risk of relapse following induction therapy is considerable and is heavily influenced by age and genetic subtype. Decisions on treating patients with relapsed or refractory disease involves careful consideration of the risk versus benefit for further therapy and there is no specific salvage regimen with proven effectiveness for these patients. Enrollment in a clinical trial should be the priority for these patients whenever possible. Therapy options are described in **Table 1**.

One approach, especially in younger adults (16-49 years) without a history of HSCT, is intensive salvage therapy followed by allo-HSCT. In the presence of active disease, there may be benefit from allo-HSCT. Other options include a short course of chemotherapy (fludarabine, cytarabine and amsarcrine [FLAMSA]) immediately prior to reduced intensity chemotherapy and allo-HSCT (Döhner 2019).

The outcome for patients who relapse after allo-HSCT during a first or second complete remission is particularly poor. No treatment algorithms have been established for the treatment of older adults with relapsed or refractory AML.

Effective treatment options are lacking for patients not able to tolerate intensive salvage chemotherapy. One option includes azacitidine and decitabine for older patients. For patients in second or third relapse, various therapeutic options are associated with complete response rates of approximately 20% and median overall survival of approximately 3 months. Targeted treatments may improve survival in these patients in the future.

Treatment Strategies for Medically Fit Elderly

Several clinical studies have shown that individuals up to 80 years of age clearly benefit from intensive treatment over supportive care only as reflected in improved complete remission and overall survival rates (Nourkeyhani 2018). Older, medically fit patients often receive the same induction regimen as their younger counterparts. Achieving a complete remission can improve quality of life by reducing the number of hospitalizations, infections and transfusion requirements and a seminal study by Löwenberg et al (2009) demonstrated a clear survival benefit for intensive therapy in patients ≥ 65 years. However, remissions are generally of short duration and the value of post-remission therapy is not established in this population (Walter 2015).

Reduced-intensity or non-myeloablative conditioning regimens have extended the age range of patients suitable for allo-HSCT to 70 to 75 years and perhaps older (**Fig. 1**) (Walter 2015).

In highly selected patients, remission following allo-HSCT can be achieved. However, while this type of HSCT can be safely performed in older patients, relapse remains a major cause of post-HSCT mortality (Wall 2017).

Treatment Strategies for Medically Unfit Elderly

AML in older adults is associated with higher therapeutic resistance and drug transport activity problems than in younger adults (Walter 2015). Despite risks, there are data from clinical trials and registry data that indicate benefit of some type of treatment in older patients (Sanford 2015).

The severe bone marrow and gastrointestinal toxicities commonly experienced with the 7 + 3 induction protocol make this regimen unsuitable for older or unfit patients. The optimal standard treatment strategy, however, remains unclear. Most commonly, these patients are treated with low-dose cytarabine (LDAC) (Döhner 2019; Stone 2019; Sanford 2015) or with the hypomethylating agents, azacitidine or decitabine (Walter 2015). The advantage of hypomethylating agents is that they are not associated with a significant risk for mucositis or organ toxicity. In a meta-analysis of 13 studies using these two regimens, complete remission rates were 15%, overall response rate 22%, 8.8 months for median relapse free survival, 6.3 months for median overall survival and 21% for 60-day mortality (Stone 2019). Responses to LDAC are not durable, and almost all patients relapse (Sanford 2015). Up to 6 courses of treatment may be needed to observe maximal response with azacitidine or decitabine; patients without response after 3 courses are unlikely to respond to or benefit from further therapy (Döhner 2019).

Novel agents with diverse mechanisms of action are under investigation in combination with LDAC and/or hypomethylating agents for the treatment of older or unfit patients with newly diagnosed AML. Ongoing trials are investigating barasertib plus decitabine, azacitidine, and low-dose cytarabine (LDAC), sapacitabine plus decitabine, and volasertib plus LDAC.

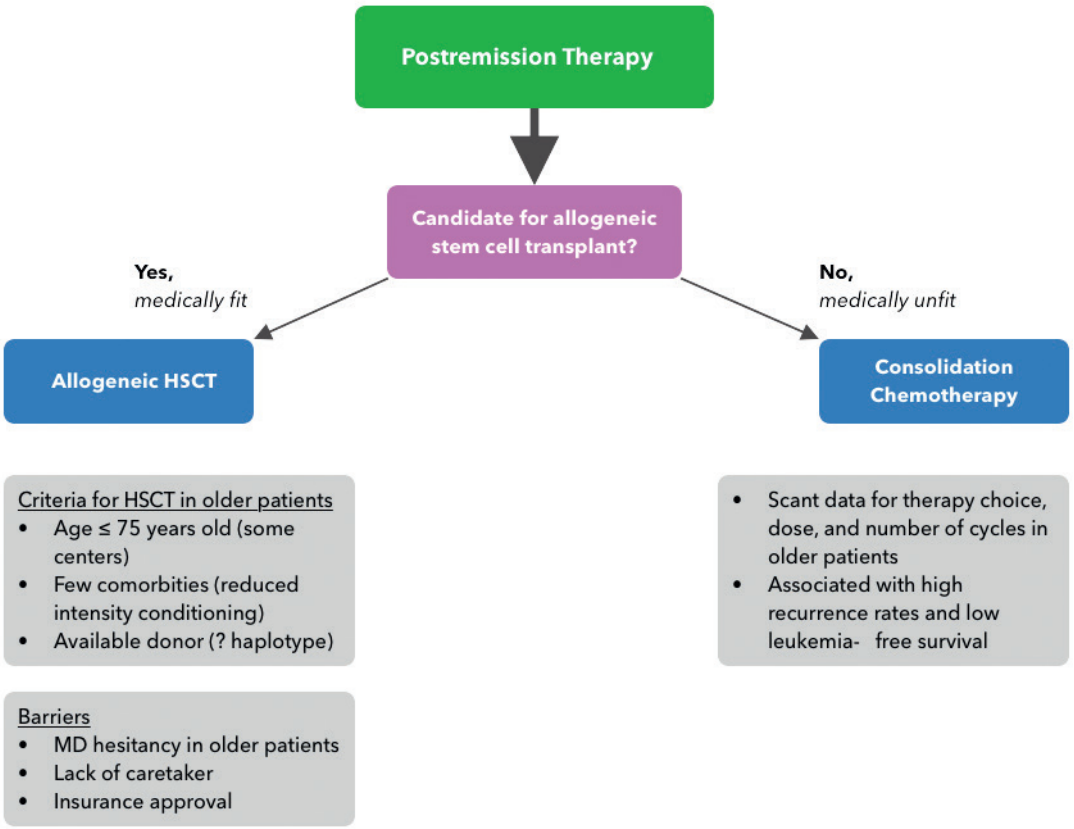

Figure 1. Considerations for consolidation/postremission therapy of older patients with AML. (Left Side): Following induction therapy, the choice of subsequent therapy is dictated by genetic risk group, the patient's physical condition and willingness to undergo hematopoietic cell transplantation (HSCT). Older patients who undergo HSCT consistently lived longer than those who did not. Reduced intensity conditioning regimens are associated with similarly good clinical outcomes as younger patients. (Right Side): Typically, consolidation consists of either high dose cytarabine or cytarabine combined with anthracycline at lower doses than used during induction; there is no consensus on the optimal number of agents, their dosages and the optimal number of cycles (Adapted from: Nourkeyhai 2018)

Treatment Strategies for Acute Promyelocytic Leukemia (APL)

Due to life-threatening complications, individuals with suspected APL should be immediately hospitalized and managed as a medical emergency. Even before a diagnosis is established, therapy with all-transretinoic acid (ATRA) and measures to counteract coagulopathy should be initiated (Sanz 2019). Patients with coagulopathy are at risk of developing cerebral stroke or major thrombosis and should be regularly monitored for corresponding signs and symptoms of these complications.

Management of coagulopathy

- Initiate ATRA when a diagnosis of APL is suspected, even if diagnostic testing is not yet fully completed
- Monitor platelet counts and routine coagulation parameters (prothrombin time, activated partial thromboplastin time, thrombin time, levels of fibrinogen and fibrinogen-fibrin degradation products)
- Transfusions of fibrinogen and/or cryoprecipitate, platelets and fresh-frozen plasma given to treat coagulopathy if APL is suspected
- Maintain fibrinogen concentration > 100 to 150 mg/dL, platelet count > 30 x 10^9/L to 50 x 10^9/L and international normalized ratio (INR) < 1.5
- Avoid invasive procedures until coagulopathy has been stabilized

Management of hyperleukocytosis (WBC count > 10 x 10^9/L) at presentation

- Initiate cytoreductive chemotherapy, even if molecular results are pending
  - ATRA + chemotherapy, idarubicin or daunorubicin alone or combined with cytarabine
  - ATRA + ATO (arsenic trioxide), cytoreduction with idarubicin or gemtuzumab ozogamicin
  - Prophylactic corticosteroids can be given, which may reduce the risk of APL differentiation syndrome

Initial treatment of APL

Recommended treatment for non-high risk patients (WBC ≤ 10 x 10^9/L) is ATRA + ATO or standard ATRA + chemotherapy

There are two treatment options for high-risk patients (WBC > 10 x 10^9/L):

- ATRA + ATO with the addition of some cytoreductive chemotherapy. (The use of ATO for high-risk patients is not approved by the FDA or EMA.)
- ATRA plus chemotherapy

Differentiation syndrome, formerly known as retinoic acid syndrome, is a life-threatening complication of therapy with differentiating agents (ATRA or ATO). The differentiation of leukemic blasts and promyelocytes induced by ATRA and/or ATO therapy may lead to cellular migration, endothelial activation and release of interleukins and vascular factors responsible for tissue damage. Approximately one quarter of patients undergoing induction therapy will develop differentiation syndrome, which is characterized by:

- unexplained fever
- hypotension
- weight gain of more than 5 kg
- acute respiratory distress and/or
- a vascular capillary leak syndrome leading to acute renal failure (Montesinos 2011)

Management of APL differentiation syndrome includes:

- Corticosteroids started immediately at clinical suspicion of incipient APL differentiation syndrome; discontinue once syndrome has resolved (corticosteroids may also be initiated as prophylaxis when leukocyte counts are high at initial presentation)
- Temporary discontinuation of differentiation therapy (ATRA or ATO)

A complete response (CR) is attained in almost all patients given standard ATRA + chemotherapy or ATRA + ATO who do not die due to complications. Treatment with ATRA or ATO should be continued until terminal differentiation with < 5% blasts in the bone marrow is achieved. The median time to CR using ATRA + ATO or chemotherapy is 4 to 5 weeks, although some patients require continuation of treatment for up to 8 to 10 weeks (Sanz 2019).

In patients with molecular persistence or molecular relapse after ATRA + chemotherapy, ATRA + ATO can be used. Where feasible, HSCT is the recommended treatment following relapse.

Therapy-related AML

Therapy-related AML occurs as a late complication (5 to 7 years) following cytotoxic therapy for a primary neoplasm or a non-neoplastic disorder. While incidences are low, they are on the rise due to an increase in the number of cancer survivors. Survival in patients with therapy-related AML remains poor mainly due to sequelae of prior therapy

and to adverse disease-related features. Allogeneic HSCT should be considered, due to the poor results with conventional chemotherapy (Döhner 2019).

New Treatment Approaches: Immunotherapy

Novel approaches using the immune system to eliminate leukemic cells in AML have only recently been applied in the clinical setting (Lichtenegger 2017) and represent a treatment option for patients not suitable for intensive treatment regimens or for patients with relapsed or refractory disease (Ramos 2015). Targeted immunotherapy relies on a suitable target antigen to avoid unwanted on-target off-tumor toxicity (Lichtenegger 2017). The use of immunotherapy in AML is complicated by different characteristics including the lack of an AML-specific target antigen, low mutational burden resulting in low endogenous immune responses and intrinsic resistance mechanisms of the leukemic blasts against immune responses (Lichtenegger 2017). Further researcher will be required to develop individualized immunotherapy in AML.

Examples of immunotherapeutic agents applied in the treatment of AML are shown below.

Agent	Comments
Antibody-drug conjugates (ADCs): gemtuzumab ozogamicin (GO); SGN-CD33A; IMGN779; SGN-CD123A; CPX-351	Clinical trials investigating clinical benefit using immunotherapy alone or in combination with chemotherapy are on-going
T cell-recruiting antibodies: MGD006; AMG 330; JNJ 63709178; Xmab14045; MCLA-117	Most agents are currently under preclinical and early clinical development for use in AML
CAR T cells	Pre-clinical and clinical trials are on-going to evaluate efficacy and safety of CAR T cells; use of CAR T cell therapy is complicated by the non-restricted expression of AML-associated antigens
Checkpoint inhibitors: Pidilizumab; ipilimumab; nivolumab; pembrolizumab; durvalumab; avelumab; atezolizumab	Show indications of being safe and well-tolerated; may provide benefit when used as monotherapy; trials currently evaluating efficacy of checkpoint inhibitors combined with a hypomethylating agent
Dendritic cell vaccination (types): Fusion of dendritic and leukemic cells; lethally irradiated and genetically modified autologous AML cells; monocyte-derived dendritic cells; dendritic-like cells generated from standardized allogeneic AML cells	Seems to be beneficial in inducing novel immune responses; combination with checkpoint inhibitors or immunomodulation agents including hypomethylating agents to enhance the immune response may be used in the future
Source: Lichtenegger 2017	

Supportive Care

Supportive care consists of helping all patients to manage both the symptoms of their condition and any side effects that may occur from treatment. Supportive care is tailored to individual patient needs and can – and should – be implemented at any time during the cancer care continuum. Further details on providing supportive and comprehensive care of the patient with acute Leukemia are provided in **Module 5**.

Management of Early Crisis

Tumor lysis syndrome (TLS)

Tumor lysis syndrome (TLS) is a condition that occurs when a large number of cancer cells combined with high-dose chemotherapy triggers a rapid lysing of the tumor cells within a short period. The breakdown of tumor cells (leukemic cells) raises levels of uric acid, potassium and phosphorus faster than the kidneys can remove them. Kidney failure and death can occur if TLS is left untreated.

The clinical manifestations and management of TLS are presented in **Module 5**.

Acute leukemic blast crisis, hyperleukocytosis, leukostasis

Leukemic blast crisis (hyperleukocytosis) is a marked elevation of Leukemia cells in the peripheral blood. Arbitrary cutoffs to define hyperleukocytosis range from 50,000 to 100,000 cells/mm^3. A subset of patients with hyperleukocytosis can develop the clinical condition of leukostasis; a life-threatening oncologic emergency where Leukemia cells (typically, but not always, immature blasts) are thought to cause organ dysfunction by impairment of microvascular perfusion. The pulmonary and CNS microvascular beds are most commonly affected.

The clinical manifestations and management of hyperleukocytosis are presented in **Module 5**.

Febrile neutropenia

Neutropenia, one of the consequences of treatment-induced myelosuppression, places the patient at risk for developing infection. Growth factors (GCSF- or GM-GSF) may be considered during induction for patients who are septic or have a life-threatening infection in an attempt to shorten the duration of neutropenia. Caution should be taken as growth factors may complicate the interpretation of marrow results and a sudden rise in neutrophils may complicate the clinical picture. For this reason, growth factors should be discontinued at least a week before a planned bone marrow aspiration. Growth factors are not recommended during induction in patients with APL as they may complicate the assessment of response. More detailed information on assessing and managing neutropenia is presented in **Module 5**.

Nursing Implications of Agents Commonly used in AML

In regards to any and all medications and chemotherapeutic agents administered, both patients and their caregivers should be provided information on:

- mechanism of action
- route and duration of administration
- possible and expected side effects
- self-care measures (**Table 4**)

Patients undergoing HiDAC should be closely monitored for changes in renal function; renal dysfunction is highly associated with increased risk of cerebellar toxicity (NCCN 2019). Assess patients for: nystagmus, dysmetria, slurred speech and ataxia before each HiDAC administration and discontinue if signs present.

A more detailed description of interventions to manage side effects of both treatment and acute Leukemia is presented in **Module 5**.

Table 4: Nursing Implications of Agents and Regimens Commonly used in Treating AML

Drug/Class/Route	Potential side effects	Management
Alkylating agents	May cause treatment-related AML	
All-trans retinoic acid (ATRA) PO	Altered ability to drive or operate machinery due to headache; hypervitaminosis A syndrome; dry skin; highly teratogenic	Apply skin moisturizer and lip balm; avoid sun exposure; Administer acetaminophen/paracetamol for headache; Advise patient to report any changes in vision or severe headache
Amsacrine Intercalating antineoplastic agent IV	Myelosuppression; mucositis/stomatitis; cardiac arrhythmias (rare)	Monitor cardiac rhythm during and after drug administration; Maintain adequate fluid & electrolyte status; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP
Arsenic trioxide IV	Prolongation of QT interval; tachycardia; hyperleukocytosis; hyperglycemia; dermatitis; thrombocytopenia; diarrhea; nausea; vomiting; chills; cough; fatigue; pyrexia; paresthesia; insomnia; may affect nutritional status	Monitor EKG and electrolytes; Monitor for signs & symptoms of hyperleukocytosis; Initiate measures to reduce bleeding risk; Inform patients of risk and symptoms of infusion reaction and to notify HCP if they occur; Provide antiemetics as needed; Provide education on measures to reduce bleeding risk & signs/symptoms of bleeding
Azacitidine Antimetabolite/ Demethylation agent SQ or IV	Tumor lysis syndrome; myelosuppression; constipation, nausea, vomiting; injection site pain/redness; pyrexia; anorexia; arthralgias, myalgias; dizziness, headache; dyspnea; renal abnormalities if given in combination with other chemotherapy agents	Myelosuppression common during first 2 cycles, less thereafter; Initiate measures to reduce infection & bleeding risks; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP
Corticosteroids (dexamethasone, prednisone)	Fatigue, thinning of skin, adrenal insufficiency, hyperglycemia, increased risk of infection, leukocytosis, bone thinning, osteoporosis, mood swings, personality changes, weight gain, decreased libido	Monitor for hyperglycemia/hypoglycemia; Educate patients on side effects including increased infection risk, signs/symptoms of infection and when to contact HCP

Drug/Class/Route	Potential side effects	Management
Cytarabine (also known as arabinofuranosyl cytidine [ARA-C]) Antimetabolite IV	Myelosuppression; skin rash; GI upset; neurotoxocity; sepsis, infections with high dose; nausea, vomiting; cytarabine syndrome (flu-like symptoms); tumor lysis syndrome	Monitor for allergic reaction, seizures, loss of consciousness; Provide antiemetics as needed; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP
High-dose cytarabine (HiDAC) IV	(as above)	Monitor renal function; monitor for signs of cerebellar toxicity and discontinue if present; discontinue agent if creatinine rises quickly
Decitabine Hypomethylating agent IV	Myelosuppression; nausea, constipation/diarrhea; cough; hyperglycemia	Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP
Doxorubicin Anthracycline IV	Nausea, vomiting; fatigue; myelosuppression; alopecia; oral ulcerations; sensitivity to sunlight; watery eyes, loss of fertility. Can cause acute and chronic cardiac toxicity	Administration of pharmacologic agents for prophylaxis of nausea/vomiting (benzodiazepines), for acute nausea/vomiting (5-HT3 receptor antagonists, dexamethasone, aprepitant, benzodiazepine); Hold ice chips in cheeks or suck on ice chips/ice cold water during administration; Assess cardiac status before drug initiation; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact; Referral to fertility specialist
Fludarabine Antimetabolite IV	Autoimmune reactions; anemia; immunosuppression; neutropenia; infections (pulmonary); neurotoxicity; hyperuricemia	Neurotoxicity can occur with higher doses generally 21-60 days after administration: advise patient/family to immediately seek medical assistance if confusion, incontinence, seizures, visual changes occur; Ensure adequate hydration, monitor electrolytes, administer allopurinol; Monitor for signs/symptoms of pulmonary infection and educate patient accordingly
G-CSF/filgrastim (Neupogen)e Cytokine SQ	Joint, bone pain; elevated WBCs; pyrexia, elevated serum alkaline; headache	Assess and medicate for pain/discomfort
Gentuzumab ozogamicin Monoclonal antibody PO	Infusion-related reactions (fever, chills, hypotension); Myelosuppression; nausea, vomiting, diarrhea; fever, chills; poor appetite; shortness of breath; hypokalemia	Premedicate to reduce severity of infusion-related reactions; Patient should not receive immunization/vaccination while taking drug; Instruct patient to contact HCP if shortness of breath or fever occur; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP
Hydroxyurea Antimetabolite PO	Myelosuppression; GI upset, anorexia; secondary malignancy; interstitial lung disease; possible renal/hepatic impairment	Monitor blood counts; Instruct patient to avoid sun exposure; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP
Idarubicin Anthracycline antitumor antibiotic IV	Myelosuppression; nausea, vomiting, diarrhea; stomatitis; alopecia; arrhythmias; skin/nail changes possible	Vesicant agent: follow appropriate SOP; Assess cardiac status before drug initiation; Urine may change color 1-2 days after administration; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP
Midostaurin Targeted therapy agent PO	Myelosuppression; nausea, vomiting, diarrhea; swelling of extremities; fatigue; headache; hyperglycemia; stomatitis; arthralgia; May cause interstitial lung disease or pneumonitis; Prolongation of QT interval	Check drug compatibilities; Monitor EKG and electrolytes; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP
Mitaxantrone Antitumor antibiotic IV	Myelosuppression; nausea, vomiting; fever; liver impairment (temporary)	Monitor lifetime maximum dose; Instruct patient to contact HCP if signs of jaundice; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding and when to contact HCP

CBC, complete blood count; GI, gastrointestinal; HCP, healthcare professional; HiDAC, high dose ARA-C; IV, intravenous; SOP, standard operating procedure; SQ, subcutaneous; WBCs, white blood cells;
Sources: NCCN 2019; https://www.ema.europa.eu/en/documents/overview/dacogen-epar-summary-public_en.pdf.; http://chemocare.com/default.aspx; http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#a-content. All sites accessed October 2019

Appendix 1: Response Criteria in AML

Category	Definition	Comment
Response		
Complete remission (CR) without minimal residual disease	If evaluated pre-treatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested and by method used; test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories
Complete remission	Bone marrow blasts <5%; absence of circulating blasts/ blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 10^9/L; platelet count ≥100 x 10^9/L	MRD +/ or unknown
Complete remission with incomplete hematologic recovery (CR1)	All CR criteria except for residual neutropenia (<1.0 x 10^9/L) or thrombocytopenia (<100 x 10^9/L)	
Morphologic Leukemia-free state	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be aplastic; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast to 5% to 25%; decrease of pretreatment bone marrow blasts by at least 50%	Important in the context of phase 1 to 2 clinical trials
Treatment failure		
Primary refractory disease	No CR or CR1 after 2 courses of intensive induction; excludes patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine generally considered as best option for patients not responding to first cycle of 7 + 3; likelihood of responding to such regimens is lower after failure
Death in aplasia	Deaths occurring ≥7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent AML	
Death from indeterminate cause	Deaths occurring before therapy completion, or <7 d following completion; or deaths occurring ≥7 d following completion of initial therapy with no blasts in blood, but no bone marrow examination available	

ANC, absolute neutrophil count; d, day(s); MFC, multiparameter flow cytometry; MRD, measurable residual disease
Adapted from: Döhner 2017

Appendix 2: Steps involved in Allogeneic Hematopoietic Cell Transplantation (HSCT)

Transplantation process step 1: Stem cell harvest or collection of donor cells

Apheresis is used to collect or harvest blood stem cells from the donor's peripheral blood system, or bone marrow or from an umbilical cord. The blood is spun at high speeds in a centrifugation chamber, which separates the stem cells from blood. The remaining blood components are reinfused into the donor.

Transplant process step 2: Conditioning regimen

Conditioning refers to the treatment the patient undergoes immediately prior to stem cell infusion. This treatment, using either ablative (high-dose chemotherapy) or reduced intensity (milder doses of chemotherapy), kills any remaining leukemic cells and weakens the immune system to reduce the risk of the body rejecting the donated cells after transplantation.

Transplant process step 3: Stem cell infusion

The donor stem cells are infused into the patient, similar to the procedure used in a blood transfusion.

Transplant process step 4: Engraftment

Engraftment, or blood count recovery, is the time required for hematopoietic stem cells to migrate from the peripheral blood to the bone marrow and begin to repopulate the bone marrow. Engraftment usually takes about 2 to 6 weeks after stem cell infusion for a return to normal blood cell counts and is usually defined as achievement of a sustained peripheral blood neutrophil count of > 500 x 106/L.

Complications of HSCT are discussed in detail in **Module 5**.

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Resources

Resources for Healthcare Professionals	
Cancer Research UK. Research into AML – Treatment.	https://www.cancerresearchuk.org/about-cancer/acute-myeloid-Leukemia-aml/research-clinical-trials/research-aml
National Health Service. Acute Myeloid Leukemia – Treatment	https://www.nhs.uk/conditions/acute-myeloid-Leukemia/treatment/
Leukemia Treatment Regimens: acute myeloid Leukemia (AML)	https://www.cancertherapyadvisor.com/home/cancer-topics/hematologic-cancers/Leukemia-treatment-regimens-acute-myeloid-Leukemia-aml/
Detailed information on agents used in the treatment of cancer	http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#a-content
UK Medical Research Council. Updates on research activities in cancer	https://mrc.ukri.org/
National Institute for Health and Care Excellence. Evidence-based guidance and updates on cancer treatment	https://www.nice.org.uk/
Information on research activities. In German	https://www.krebsgesellschaft.de/
Search information on National Cancer Institute (NCI) supported clinical trials	https://www.cancer.gov/about-cancer/treatment/clinical-trials/advanced-search
KNOW AML: The first global acute myeloid Leukemia (AML) awareness initiative.	https://know-aml.com/en/information-support
Resources for Patients and Families	
Information on chemotherapy agents including managing side effects. Sponsored by Cleveland Clinic, US	http://chemocare.com/default.aspx
Patient Power. Acute Myeloid Leukemia – Supportive Care	https://www.patientpower.info/acute-myeloid-Leukemia/treatment-journey/supportive-care
Cancer Champions. Chemotherapy, Immunotherapy, Targeted Therapy. What's the difference?	https://cancer-champions.com/chemotherapy-immunotherapy-targeted-therapy-whats-the-difference/
Information on acute Leukemia/cancer. In Dutch and English	https://www.hovon.nl
Information on general cancer topics and research highlights. In German	https://www.krebsgesellschaft.de/
KNOW AML: The first global acute myeloid Leukemia (AML) awareness initiative.	https://know-aml.com/en/information-support

Quick Facts

- The outcome of ALL is very closely related to the age of the patient: while cure rates reach 90% in children, < 10% of elderly patients are cured of their disease
- Pre-phase treatment, usually with corticosteroids and vincristine or cyclophosphamide, provides management and prevention of metabolic, infectious and hemorrhagic complications before induction is initiated
- There is a strong correlation between the level of measureable residual disease (MRD) and risk for relapse, and the presence of MRD at various stages throughout the treatment process has prognostic implications
- Vincristine, corticosteroids, L-asparaginase (when possible) and/or cyclophosphamide are the "backbone" agents used in remission induction treatment
- New treatment options for patients with MRD+ disease (blinatumomab, after prior conventional chemotherapy) and patients with relapsed/refractory disease (blinatumomab, inotuzumab ozogamycin)
- Serious and/or life-threatening effects can occur if early crisis syndromes such as inflammatory/cytokine release syndrome, tumor lysis syndrome and hyperleukocytosis are not recognized early and treated promptly and appropriately
- Supportive therapy (e.g., treatment of infections, administration of blood products, psychosocial interventions) should be initiated early whenever necessary

[1] Because new agents are continually being developed and evaluated for use in ALL, treatment options change quickly. The information contained in this module will be regularly updated to reflect these developments.

Introduction: Treatment Strategies

Successful treatment of acute lymphoblastic Leukemia (ALL) consists of the control of bone marrow and systemic disease and the treatment (or prevention) of sanctuary-site disease, particularly disease located in the central nervous system (CNS). Therefore, the cornerstone of treatment includes systemically administered combination chemotherapy with CNS preventive therapy. CNS prophylaxis is achieved with chemotherapy (intrathecal and/or high-dose systemic therapy) and, in some cases, cranial radiation therapy (NCCN 2019; Terwilliger 2017).

Treatment with a curative aim involves achievement of complete response (CR) followed by allogeneic hematologic stem cell transplantation (allo-HSCT) (Hoelzer 2016). When the duration of first CR is long (> 2 years), re-induction with a standard induction regimen is appropriate at relapse. However, should the first CR be short or the ALL is refractory to treatment, consideration of entering the patient on a trial using novel agents that may be non-cross-resistant with chemotherapy should be made (Hoelzer 2016). Despite the high rates of CR, the cure rates for ALL are only 40% to 50% because of relapses (Sive 2012).

In light of the rarity of adult ALL, the complexity and unique complications of treatment, and the frequent implementation of allo-HSCT, treatment should take place at a center specialized in managing patients with ALL as survival appears to be superior when patients receive their treatment at an academic/research hospital (Wieduwilt 2018). Entry into a clinical trial is highly desirable to assure state-of-the-art treatment and maximal retrieval of data for analysis and evaluation.

Centers may differ in treatment protocols and nomenclature, but the main constituents of treatment for ALL are:

- Remission induction
- CNS prophylaxis and treatment
- Consolidation
- Allo-HSCT
- Long-term maintenance therapy (also referred to as post-remission or remission continuation)

Most resources divide recommendations for therapy of ALL into two categories: treatment of Philadelphia negative (Ph-) ALL and treatment of Philadelphia positive (Ph+) ALL. Hence, treatment strategies presented in this Module refer to Ph- disease unless otherwise stated.

Consideration of patient-related factors

The outcome of ALL is very closely related to the age of the patient; cure rates in childhood ALL range from 80% to 90% decreasing to < 10% in elderly/frail patients (Hoelzer 2016). Age-related protocols are in use in which age limits are mainly directed by the hematological and non-hematological treatment toxicities. Regarding treatment considerations, age is separated into the following general groups for adults:

- Adult ALL protocols: young adults (roughly 15 to 39 years); adults 35 to 40 up to ≤ 55 to 60 years of age
- Elderly ALL protocols: > 55 to 60 years
- Frail patients (not suitable for intensive therapy): generally older than 70 to 75 years

An accurate and thorough assessment of the older patient is necessary to assess their ability to undergo aggressive therapy. Chronological age alone does not provide sufficient information on physical status or level of fitness. Other determinants to consider are:

- presence of medical comorbidities
- cognitive function
- polypharmacy
- functional status
- nutrition status
- mental health/presence of depression
- presence of social support

A dedicated geriatric assessment tool should be used to obtain accurate data on the patient's level of fitness, which is invaluable in predicting treatment-related toxicities and outcomes (Klepin 2011).

The pronounced myelosuppression from both ALL and ALL therapy means that older patients will require supportive therapy with blood product transfusions, granulocyte colony-stimulating factor (G-CSF) and prophylactic antibiotics during remission induction.

The various patient-related risk factors with a potential to affect treatment decisions are discussed in **Module 2**.

Pre-phase treatment

Treatment should start immediately once a diagnosis is established. A pre-phase therapy with corticosteroids (usually prednisone 20 to 60 mg/day or dexamethasone 6 to 16 mg/day) alone or in combination with another drug (e.g., vincristine, cyclophosphamide), is often given together with allopurinol and hydration for about 5 to 7 days. The pre-phase therapy allows for management and prevention of metabolic, infectious and hemorrhagic complications before starting induction therapy (see Management of Early Crisis later in this Module). Activities to preserve fertility are also conducted during this time. The response to pre-phase therapy will allow the completion of the diagnostic workup and analysis of results (Hoelzer 2016). Response to pre-phase therapy defines the chemosensitivity of ALL and a possible prediction of treatment response. The average length of total treatment for ALL varies between 1.5 and 3 years.

Measureable Residual Disease

Complete remission, as defined by conventional morphological criteria, is a highly heterogeneous state with a wide range of residual Leukemia burden. In this light, many patients in complete remission (CR) actually have residual disease that will lead to clinically evident relapse if additional treatment is not administered. Studies on ALL in adults indicate a strong correlation between measureable residual disease (also referred to as minimal residual disease [MRD]) and risk for relapse, and the prognostic significance of presence throughout the treatment process (**Table 1**). Therefore, evaluation of MRD will often be performed:

1) At early time points such as following induction. Post-induction MRD can serve as an independent predictor of relapse even in patients considered to be standard risk defined by other methods. Being MRD+ will render these patients high risk
2) After consolidation therapies, MRD has been shown to be a key prognostic significance and offer possibility to adjust post-consolidation treatment or provide alternative therapy
3) Sequentially beyond consolidation to detect impending morphologic relapse (Döhner 2017).

[See Module 2 for more information on MRD.]

Table 1: Response Parameters in ALL according to Measureable Residual Disease

Terminology	Definition
Complete hematological remission (CR)	Leukemic cells not detectable by light microscopy in bone marrow (<5% blasts), peripheral blood, cerebral spinal fluid
Complete molecular remission/MRD negativity (molCR)	Patient in CR MRD not detectable by sensitive molecular probes
Molecular/MRD response, less than molCR (molR)	Patient in CR, not in molCR Low-level non-quantifiable MRD Assessable by MFC
Molecular/MRD relapse (molRel)	Patient still in CR, prior molCR/molR Loss of molCR/molR status Assessable by MFC, also assessable by other techniques, in EU especially PCR (or NGS) is being used
Relapse	Loss of CR status Hematological relapse (>5% blasts in bone marrow) Extramedullary relapse (CNS, other site)

CNS, central nervous system; MFC, multiparameter flow cytometry; MRD, minimal residual disease
Adapted from: Hoelzer 2016

Remission Induction

The goal of induction therapy is to induce a CR, or a molCR/good molecular response (Appendix 1), by eradicating leukemic cells in the bone marrow. In addition to disease characteristics identified at diagnosis of ALL, response to initial therapy predicts outcome; a measurement of response is usually performed within 6 to 16 weeks of the initiation of chemotherapy. Following appropriate induction therapy, approximately 60% to 80% of adults with ALL usually achieve a CR (PDQ 2019). The persistence of MRD following initial therapy has a strong association with disease-free and overall survival (OS) (Terwilliger 2017).

The remission induction regimen generally combines chemotherapy with prednisone. Other drugs such as asparaginase or cyclophosphamide may be added. Hence, drugs that serve as the backbone of ALL induction treatment are:

Vincristine, an anthracycline (e.g., daunorubicin or doxorubicin), corticosteroids (e.g., prednisone or dexamethasone), with or without L-asparaginase and/or cyclophosphamide.

L-asparaginase is the only drug used specifically in ALL, most commonly in pediatric patients. Pegylated asparaginase (PEG-Asp) has the advantage of a significantly longer period of asparagine depletion. However, the role of L-asparaginase is a challenge in some adults due to increased risk of adverse events. For this reason, asparaginase may be omitted (or administered in a reduced dose) in treatment protocols used in patients over the age of 40 (Terwilliger 2017). Dexamethasone is often preferred to prednisone, since it penetrates the blood-brain barrier and acts on resting leukemic blast cells (Hoelzer 2016). However, dexamethasone is associated with more adverse events compared to prednisone (Terwilliger 2017).

Examples of commonly used induction remission regimens are shown in **Table 2**.

Table 2: Examples of Remission Induction Chemotherapy Treatment Protocols Commonly used in Adults ≥ 40 to about 65 years with ALL	
Hyper-CVAD +/- Rituximab	**Cycles 1, 3, 5, and 7** **Days 1–3:** Cyclophosphamide 300mg/m^2 IV + MESNA 600mg/m^2/day **Days 1–4 and 11–14:** Dexamethasone 40mg orally daily, +/- **Days 1 and 8:** Rituximab 375mg/m^2 IV **Day 4:** Doxorubicin 50mg/m^2 IV over 24 hours **Days 4 and 11:** Vincristine 2mg IV. **Cycles 2, 4, 6, and 8** **Day 1:** MTX 200mg/m^2 IV followed by 800mg/m^2 continuous IV followed by leucovorin 50mg IV after completion of MTX until MTX level <0.05uM **Days 2–3:** Cytarabine 3g/m^2 (1g/m^2 for patients >60 years old) IV, +/- **Days 1 and 8:** Rituximab 375mg/m^2 IV **CNS Prophylaxis** **Day 2:** MTX 12mg IT **Day 8:** Cytarabine 100mg IT
Sources: Kantarijan 2004; Thomas 2010	
MRC UKALLXII/ECOG2993	**Induction** **Phase 1 (Weeks 1–4):** **Days 1, 8, 15, and 22:** Daunorubicin 60mg/m^2 IV + vincristine 1.4mg/m^2 IV **Days 1–28:** Prednisone 60mg/m^2 orally daily **Day 15:** MTX 12.5mg IT **Days 17–28:** L-asparaginase 10,000IU IV or IM. **Phase 2 (Weeks 5–8):** **Days 1, 15, and 29:** Cyclophosphamide 650mg/m^2 IV **Days 1–4, 8–11, 15–18, and 22–25:** Cytarabine 75mg/m^2 IV **Days 1–28:** 6-Mercaptopurine 6mg/m^2 orally daily **Days 1, 8, 15, and 22:** MTX 12.5mg IT. **Intensification** **Days 1, 8, and 22:** MTX 3g/m^2 IV **Days 2, 9, and 23:** L-asparaginase 10,000IU IM or IV + leucovorin rescue **Consolidation** **Cycle 1:** **Days 1–5:** Etoposide 100mg/m^2 IV + cytarabine 75mg/m^2 IV **Days 1, 8, 15, and 22:** Vincristine 1.4mg/m^2 IV **Days 1–28:** Dexamethasone 10mg/m^2 orally daily. **Cycle 2 (4 Weeks After Cycle 1):** **Days 1–5:** Cytarabine 75mg/m^2 IV + etoposide 100mg/m^2 IV **Cycle 3 (4 Weeks After Cycle 2):** **Days 1, 8, 15, and 22:** Daunorubicin 25mg/m^2 IV **Day 29:** Cyclophosphamide 650mg/m^2 IV **Days 31–34 and 38–41:** Cytarabine 75mg/m^2 IV **Days 29–42:** Thioguanine 60mg/m^2 orally daily. **Maintenance:** Vincristine 1.4mg/m^2 IV every 3 months Prednisone 60mg/m^2 orally for 5 days every 3 months 6-Mercaptopurine 75mg/m^2 orally daily MTX 20mg/m^2 orally or IV once weekly. Continue for 2.5 years from start of intensification therapy.
Source: Rowe 2005	
IT, intrathecal; IV, Intravenous; a Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome and neurologic toxicities. The instructions for blinatumomab product preparation (including admixing) and administration should be strictly followed to minimize medication errors. Close monitoring of the patient during agent administration is essential.	

Post-remission Consolidation

The rationale for employing treatment after remission is to use systemic high-dose therapy to reach sufficient drug levels in sanctuary sites, such as the CNS. Most protocols employ 6 to 8 courses that contain either high-dose methotrexate or high-dose cytarabine +/- asparaginase.

High-dose cytarabine	1 to 3 g/m^2 for 4 to 12 doses
High-dose methotrexate	1 to 1.5 g/m^2 up to 3 g/m^2

Central Nervous System (CNS) Prophylaxis

While few patients (about 3% to 7%) have central nervous system (CNS) involvement at the time of diagnosis, many will eventually develop CNS involvement if CNS-directed treatment is not initiated. This means, all patients with ALL should receive CNS prophylaxis (Hoelzer 2016). The aim of CNS prophylaxis and/or treatment is to clear leukemic cells within sites that cannot be readily accessed by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse. Factors associated with increased risks for CNS Leukemia include:

- Mature B-cell immunophenotype
- T-cell immunophenotype
- High presenting WBC counts
- Elevated serum LDH levels (Lazarus 2006)

Effective CNS prophylaxis is essential in patients without involvement at the time of treatment initiation. Treatment modalities for CNS prophylaxis used as single agents or in combination include:

- CNS irradiation (skull only)
- intra-thecal methotrexate
- mono- or intra-thecal triple therapy (usually methotrexate, steroids, cytarabine)
- systemic high-dose therapy with either methotrexate and/or cytarabine (NCCN 2019; Hoelzer 2016)

Using these therapies, CNS relapse rate in recently conducted clinical trials could be reduced from 10% to < 5% (Hoelzer 2016). Patients who present with CNS involvement are treated with the standard chemotherapy regimen and additional intra-thecal applications until blasts are no longer present in the spinal fluid. To be effective, CNS prophylaxis should be administered at intervals throughout the course of therapy.

Adverse events associated with cranial irradiation include:

- Neurocognitive dysfunctions
- Secondary CNS tumors
- Other long-term complications

Allogeneic Hematopoietic Cell Transplantation

Treatment options following achievement of a complete response include consolidation and maintenance chemotherapy or allo-HSCT. Allo-HSCT has continued to be the best option for high-risk patients and patients with relapsed/refractory disease and is considered the standard of care and best chance for a durable response (**see Appendix 2**). The benefits of allo-HSCT in standard-risk adults is unclear. However, here the evaluation of risk using MRD can be a prognostic marker to re-stratify patients to high-risk, making them candidates for allo-HSCT (Terwilliger 2017). Allo-HSCT should be considered in all patients who relapse. [More information on managing patients undergoing allo-HSCT is presented in **Module 5**.]

Maintenance Therapy

The goal of maintenance therapy is to prevent disease relapse after post-remission induction and consolidation. Generally, maintenance regimens are based on daily 6-mercaptopurine (6-MP) and weekly methotrexate (often combined with periodic vincristine and corticosteroids) for 2 to 3 years.

There seems to be a relationship between myelosuppression occurring during maintenance therapy and outcome: outcomes are better in those patients who become myelosuppressed than in patients who have higher neutrophil counts (Schmiegelow 2010).

Treatment of Relapsed ALL

Patients who experience a relapse after remission usually die within 1 year, even if a second CR is achieved. Allo HSCT may be a consideration if the patient's medical condition permits, a suitable donor is available, and the patient is willing to undergo the procedure.

While 85% to 90% of patients go into remission after induction treatment, there are patients that are refractory to this treatment and a large percentage of patients relapse after achieving CR. Options for treatment of relapsed disease include augmented cytotoxic chemotherapy,

reformulated single-agent chemotherapy, allo-HSCT, novel monoclonal antibodies and CAR Ts (**Table 3**).

In patients with relapsed and refractory disease, particularly those with multiple relapses, toxicity of multi-agent cytotoxic therapy may limit options. For this reason, single-agent salvage therapy has been used. The most promising option to prolong survival and possibly cure ALL in these patients is allo-HSCT, although recently developed novel antibodies (e.g., blinatumomab (blinatumomab is NOT a monoclonal antibody, it is a BiTE, a bispecific T-cell engager molecule, it is a construct based on the antigen binding sites of 2 monoclonal antibodies and its structure is not that of an antibody), inotuzumab, ozogamicin) now offer a chance for cure (Terwilliger 2017). Anti-CD19 CAR T agents have been recently approved for treatment of relapsed and refractory ALL, in patients up to the age of 25 years.

Agents and regimens used as treatment of relapse/refractory disease for B-cell and T-cell ALL are as described above and in **Table 3**.

Table 3: Examples of Treatment Regimens for Refractory or Relapsed ALL in Adults

Clofarabine-Containing Regimens (for B-ALL)	**Induction** **Days 1–5:** Clofarabine 40mg/m^2 IV + etoposide 100mg/m^2 IV + cyclophosphamide 440mg/m^2 IV **Consolidation** **Days 1–4:** Clofarabine 40mg/m^2 IV + etoposide 100mg/m^2 IV + cyclophosphamide 440mg/m^2 IV
Cytarabine-containing Regimens	**Days 1–5:** Cytarabine 3g/m^2 IV **Day 3:** Idarubicin 40mg/m^2
Alkylator-containing Regimens	**Days 1–3:** Mitoxantrone 8mg/m^2 IV daily **Days 1–5:** Etoposide 100mg/m^2 IV daily + ifosfamide 1.5g/m^2 IV daily
Nelarabine (for T-ALL)	**Days 1, 3, and 5:** Nelarabine 1.5g/m^2/day IV Repeat cycle every 21 days.
Augmented Hyper-CVAD	**Cycles 1, 3, 5, and 7** **Day 1:** Pegaspargase 2,500units/m^2 IV **Days 1–3:** Cyclophosphamide 300mg/m^2 IV + MESNA 600mg/m^2 IV **Day 4:** Doxorubicin 50mg/m^2 IV **Days 1, 8, and 15:** Vincristine 2mg IV **Days 1–4 and 15–18:** Dexamethasone 80mg IV or orally. **Cycles 2, 4, 6, and 8** **Day 1:** MTX 1g/m^2 IV with leucovorin 50mg IV after completion of MTX, followed by leucovorin 15mg IV **Days 2–3:** Cytarabine 3g/m^2 IV **Day 5:** Pegaspargase 2,500units/m^2 IV **Maintenance** Mercaptopurine 50mg orally + MTX 20mg/m^2 orally + vincristine 2mg IV + prednisone 200mg orally
Vincristine Sulfate Liposome Injection	Liposomal vincristine sulfate 2.25mg/m^2 IV weekly until response, progression, toxicity, or pursuit of HSCT
Blinatumomab[a] (for B-ALL; preferred)	**Cycle 1** **Days 1–7:** Blinatumomab[a] 9mcg/day IV **Days 8–28:** Blinatumomab[a] 28mcg/day IV **Subsequent Cycles** **Days 1–28:** Blinatumomab[a] 28mcg/day IV Repeat cycle every 42 days

IT, intrathecal; IV, Intravenous; [a] Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome and neurologic toxicities. The instructions for blinatumomab product preparation (including admixing) and administration should be strictly followed to minimize medication errors. Close monitoring of the patient during agent administration is essential

Sources: DeAngelo 2007; Faderl 2011; O'Brien 2013; Topp 2012; Topp 2011

Treatment of Philadelphia positive (Ph+) ALL

Treatment of adult patients with Ph+ ALL generally includes adding a tyrosine kinase inhibitor (TKI) (ponatinib, imatinib, dasatinib) to regimens used to treat Ph- ALL (**Table 4**). According to the NCCN Guidelines (2019), regimens for induction for Ph+ ALL include:

- TKI + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) alternating with high-dose methotrexate and cytarabine
- TKI + multiagent chemotherapy (daunorubicin, vincristine, prednisone, cyclophosphamide)
- TKI + corticosteroids
- TKI + vincristine + dexamethasone

Allo HSCT with standard myeloablative conditioning is recommended as the best treatment option in Ph+ patients with a suitable donor in first complete remission (Hoelzer 2016).

Regimens for maintenance in this population, as described in the NCCN Guidelines (2019) include:

- TKI (imatinib, dasatinib, nilotinib, ponatinib) to maintenance regimen
- Monthly vincristine/prednisone pulses (for 2 to 3 years), +/- weekly methotrexate + daily 6-MP as tolerated

Imatinib mesylate is often incorporated into the therapeutic plan for older patients with Ph+ ALL. This agent is an inhibitor of the BCR-ABL tryrosine kinase and has been shown to have clinical activity as a single agent in this population. More commonly, imatinib mesylate is used in combination with chemotherapy regimens.

TKIs, most notably imatinib, may be beneficial as maintenance therapy following HSCT in Ph+ patients to reduce relapse risk and provide more durable remission. Relapse soon after induction is associated with poorer survival outcomes in this population (NCCN 2019). Recommended regimens for relapsed or refractory Ph+ ALL often combine a TKI with any of the induction regimens not previously given (NCCN 2019).

Table 4: Examples of Treatment Protocols Commonly used in Adults ≥ 40 years, Ph+

Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) + Tyrosine Kinase Inhibitors (TKIs)	**Induction** 4 cycles Hyper-CVAD alternating with 4 cycles of high dose cytarabine and MTX **Days 1–14 of each cycle:** Dasatinib 50mg orally twice daily OR imatinib 400mg orally daily **OR** **Day 1:** Cyclophosphamide 1,200mg/m^2 IV **Days 1–3:** Daunorubicin 60mg/m^2 IV **Days 1–21:** Prednisolone 60mg/m^2 orally **Days 1, 8, 15, and 22:** Vincristine 1.3mg/m^2 IV bolus **Days 8–63:** Imatinib 600mg orally **Day 29:** MTX 15mg IT, cytarabine 40mg IT, dexamethasone 4mg IT **OR** **Pretreatment for 7 days:** Prednisone at increasing doses from 10–40mg/m^2/day **Days 1–45:** Imatinib 800mg orally daily + prednisone 40mg/m^2 daily (patients >60 years). **OR** **Pretreatment for 7 days:** Prednisone at increasing doses from 10–60mg/m^2/day **Days 1–24:** Prednisone 60mg/m^2 daily (max 120mg daily) **Days 1–48:** Dasatinib 70mg orally twice daily **Days 22 and 43:** MTX IT **Days 25–32:** Prednisone taper.
	Consolidation Allogeneic hematopoietic cell transplant (HSCT), consider post-HSCT TKI **OR** Continue multi-agent chemotherapy + TKI
	Maintenance MTX weekly + 6-MP daily + vincristine pulse monthly + prednisone pulse monthly for 2 to 3 years
	Relapsed or Refractory Disease

Table 4: Examples of Treatment Protocols Commonly used in Adults ≥ 40 years, Ph+	
Dasatinib[a] (TKI) (preferred)	Dasatinib 140mg orally daily. Continue until disease progression or unacceptable toxicity
Nilotinib[b] (TKI)	Nilotinib 400mg orally twice daily. Continue until disease progression or unacceptable toxicity
Imatinib (TKI) (preferred)	Imatinib 600mg orally daily. Continue until disease progression or unacceptable toxicity
Ponatinib[c] (TKI) (preferred)	Ponatinib 45mg orally daily. Continue until disease progression or unacceptable toxicity

IT, intrathecal; IV, intravenous. [a] For patients with mutations Y253H, E255K/V or F359V/C/I. [b] For patients with mutations F317L/V/I/C, T315A or V299L [c] Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs, but is associated with a high frequency of serious vascular events. The FDA indications are for the treatment of adult patients with T3151-positive PH+ ALL and for the treatment of adult patients with PH+ ALL for whom no other TKI therapy is indicated
Sources: Lilly 2010; Ottmann 2007a; Kantarjian 2006; Ottmann 2002; Cortes 2013
Please note that trials on blinatumomab monotherapy in R/R Ph+ ALL (Martinelli, JCO2017) and of combination therapy with TKIs in the frontline setting have shown efficacy and tolerability. The use in combination with dasatinib in frontline Ph+ is the first chemo-free approach with very promising data (Chiaretti, EHA and ASH 2019).

Treatment Strategies in Elderly/ Medically Unfit Patients

The incidence of ALL is increasing in persons older than 50 (Guru 2015) and the percentage of ALL deaths is highest among people aged 65 to 74 (SEER 2019). Older patients, especially those aged 65 years and older, with ALL commonly have multiple comorbidities and poor performance status and are less likely to participate in clinical trials. Factors contributing to poor outcomes in older patients include the inability to deliver optimal therapy and the higher death rate during the induction phase of treatment (Sawalha 2018).

Treatment protocols designed for older or frail patients are generally less intensive and based on corticosteroids, vincristine and asparaginase with avoidance of anthracyclines and alkylating agents to reduce early treatment-related deaths (**Table 5**). Results of several clinical studies indicate that these types of less intensive treatments in older patients produced CR rates of 71%, early death rates decreased to 15% and OS was significant at 33 months. These results highlight the need for treatment, irrespective of patient age.

Prophylactic CNS treatment should be given to older patients at intervals throughout induction and during post remission therapy, as would be the case with younger adults.

Blinatumomab has been shown to demonstrate an efficacy/tolerability profile in elderly, which is quite comparable to that in younger adults, with a caveat for increased neurotoxicity. (Kantarjian, 2016).

Table 5: Induction Regimens for Adults aged ≥ 65 Years
Low intensity Vincristine + prednisone Prednisone, vincristine, methotrexate, 6-mercaptopurine (POMP)
Moderate intensity Idarubicin, dexamethasone, vincristine, cyclophosphamide, cytarabine +/- rituximab Vincristine, dexamethasone, idarubicin, cyclophosphamide, cytarabine, methotrexate and L-asparaginase Doxorubicin, vincristine, dexamethasone, cytarabine, cyclophosphamide Dexamethasone, doxorubicin, vincristine, methotrexate, cytarabine, L-asparaginase, intrathecal chemotherapy
High intensity Hyper-CVAD with dose reduced cytarabine (1 gm/m^2)
Sources: Gokbuget 2012; Ribera 2016; Hunault-Berger 2011; Larson 1998

HSCT (possibly with reduced-intensity conditioning) may be a consideration in those older medically fit individuals achieving remission. HSCT in this population should only be performed at centers with transplant expertise and appropriate and adequate resources.

Approximately half of elderly patients are Ph+. Here, targeted therapies with TKIs now provide improved outcomes as these agents may be better tolerated than chemotherapy in older patients (**Table 6**).

Table 6: Induction Regimens for Adults aged ≥ 65 Years with Ph+ ALL

Low intensity TKI (imatinib, dasatinib, nilotinib +/- corticosteroids TKI (dasatinib, imatinib) + vincristine, dexamethasone
Moderate intensity TKI (dasatinib, nilotinib) with multiagent chemotherapy (vincristine, dexamethasone, methotrexate, cytarabine, asparaginase)
High intensity TKI (dasatinib, ponatinib) with HyperCVAD with dose-reduced cytarabine (1 gm/m^2)

TKI, tyrosine kinase inhibitor
Sources: Foa 2011; Rousselot 2016; Jabbour 2015; O'Brien 2008; Ottmann 2007b

New Treatment Approaches

New and novel approaches to treatment of adult ALL are being investigated in an effort to improve outcomes achieved with chemotherapy and allo-HSCT (**Table 7**). Particularly for B-lineage ALL, therapies with antibodies are being studied and for Ph+ ALL, targeted therapy with TKIs.

Now that the immunophenotype and genotype of a patient's Leukemia can be characterized, targeted therapy may have a positive effect on remission and survival. Monoclonal antibodies may also trigger external pathways, such as ADCC, CDC.. Immunoconjugates, such as inotuzumab ozogamicin, bind to leukemic cells, are internalized and release a cytoxin that kills leukemic cells. Therapy with BiTE agents, such as blinatumomab, cause direct activation of T cells against blasts. These new approaches to the treatment of ALL may provide adults with the same favorable treatment prospects as those currently available to pediatric patients with ALL.

Table 7: Novel Treatments under Investigation for ALL

Agent	Possible indication
Monoclonal antibodies	
Blinatumomab	
CD22	B-cell
Epratuzumab	Relapsed/refractory, B-cell
Inotuzumab ozogamicin	Relapsed/refractory, patients > 60 years
Moxetumomab pasudodotox	Relapsed/refractory
Pasudotox	Relapsed/refractory
B-CD20 (rituximab)	CD20-positive Leukemia
Ofatumumab	CD20-positive ALL
Obinutuzumab	CD20-positive pre B-cell ALL
REGN1979	Relapsed/refractory
C-CD19	B-cell ALL
Denintuzumab mafodotin	Relapsed/refractory
ADCT-402	Relapsed/refractory
ADCT-301	Relapsed refractory
Protease inhibitors	
Bortezomib	Relapsed/refractory in combination with chemotherapy
3-JAK inhibitor	
Ruxolitinib	Newly diagnosed high-risk B-cell with CRLF2 rearrangements
6-Chimeric antigen receptor (CAR) T cells	Relapsed/refractory as a bridge to allo-HSCT or to produce durable remission
P13K/mTOR inhibitors	Relapsed/refractory

Source: Terwilliger 2017

Supportive Care

Supportive care consists of helping all patients to manage both the symptoms of their condition and any side effects that may occur from treatment. Supportive care is tailored to individual patient needs and can – and should – be implemented at any time during the cancer care continuum. Further details on providing supportive and comprehensive care of the patient with ALL are provided in **Module 5**.

Management of Early Crisis

Tumor lysis syndrome (TLS)

Tumor lysis syndrome (TLS) is a condition that occurs when a large number of cancer cells combined with high-dose chemotherapy brings a rapid lysing of the tumor cells within a short period. The breakdown of tumor cells (leukemic cells) raises levels of uric acid, potassium and phosphorus faster than the kidneys can remove them. Kidney failure and death can occur if TLS is left untreated.

The clinical manifestations and management of TLS are presented in **Module 5**.

Inflammatory/cytokine release syndrome (CRS)

This syndrome can be life-threatening and can occur after the administration of of the following therapeutic options, including:

- Naked antibodies such as rituximab, alemtuzumab and OKT3
- Bispecific antibodies such as blinatumomab
- Adoptive T-cell therapies such as CAR T cells
- Infusion of haploidentical mononuclear cells to treat refractory Leukemia

The clinical manifestations and management of CRS are presented in **Module 5**.

Hyperleukocytosis (WBC count > 10 x 10^9/L)

Leukemic blast crisis (hyperleukocytosis) is a marked elevation of Leukemia cells in the peripheral blood. Arbitrary cutoffs to define hyperleukocytosis range from 50,000 to 100,000 cells/mm^3. While hyperleukocytosis is relatively uncommon in ALL, a subset of patients with this condition can develop leukostasis; a life-threatening oncologic emergency where Leukemia cells (typically, but not always, immature blasts) are thought to cause organ dysfunction by impairment of microvascular perfusion. The pulmonary and CNS microvascular beds are most commonly affected.

The clinical manifestations and management of CRS are presented in **Module 5**.

Febrile neutropenia

Neutrophils are critical in providing host defense against infection, particularly bacterial and fungal infections. Neutropenia is a common side effect of both chemotherapy and ALL. Duration and nadir of neutropenia are correlated with the incidence of fever and infections, which not only cause significant morbidity and mortality but may also compromise further therapy (Heinz 2017). Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection, because signs and symptoms of inflammation are typically attenuated.

The clinical manifestations and management of febrile neutropenia are presented in **Module 5**.

Nursing Implications of Agents Commonly used in ALL

In regards to any and all medications and chemotherapeutic agents administered, both patients and their care-givers should be provided information on:

- mechanism of action
- route and duration of administration
- possible and expected side effects
- self-care measures

Agents requiring special precautions

Inotuzumab: Cytoreduction (hydroxyurea or a combination of steroids and vincristine) should be considered with WBC > 10,000 cells/mL.

Blinatumomab: Cytoreduction (with steroids) should be considered with WBC > 15,000 cells/mL as high tumor burden may increase the risks of toxicity. Monitor patients for cytokine release syndrome (CRS). Monitor patients intensely for neurologic toxicity, which may include confusion, word-finding difficulty, somnolence, ataxia, tremor, seizure or syncope at the first sign of any of these events.

Tisagenlecleucel: Severe cytokine release syndrome and/or neurologic toxicity may occur. Prophylaxis with anti-seizure medication may be considered during the first month after tisagenlecleucel infusion. Severe neutropenia, T-cell depletion and B-cell aplasia can occur and can be managed with growth factor, prophylactic antimicrobial therapy or intravenous immunoglobulin.

Asparaginase: There is a significant incidence of hypersensitivity reactions with asparaginase products in some regimens. Of particular concern are more severe allergic reactions, urticarial, or anaphylaxis as these

reactions can be associated with neutralizing antibodies and lack of efficacy (NCCN 2019). Asparaginase should be permanently discontinued in patients who exhibit a severe anaphylactic reaction. There are 3 formulations of asparaginase in clinical use and agents may be changed in patients who have developed an allergic reaction. Anti-allergy premedication should be administered.

6- mercaptopurine (6-MP). Several factors can affect 6-MP bioavailability and subsequently impact on patient care. Oral 6-MP can have highly variable drug and metabolite concentrations among patients, which can be affected by age, gender and genetic polymorphisms. Concomitant use of some chemotherapeutic agents such as methotrexate can alter toxicity. There is some controversy surrounding the effect of dairy products and fasting state on 6-MP metabolism leading to the conclusion that drug adherence is more important than either of these factors (Maese 2018). Dose adjustments may be necessary in patients with hepatotoxicity or myelosuppression or in those with heterozygosity at the TPMT gene.

Methotrexate: Leucovorin is usually administered 12 to 24 hours after methotrexate administration to selectively "rescue" normal cells from the adverse effects of methotrexate caused by inhibition of production of reduced folates.

Table 8: Nursing Implications of Agents and Regimens Commonly used in Treating ALL

Drug/Class/ Route	Potential side effects	Management
6-mercaptopurine (6-MP) (Thioguanine) Antimetabolite Oral	Myelosuppression: onset 7-10 days after administration; hepatotoxicity at doses > 2.5 mg/kg/day	Monitor CBC; Monitor for signs/symptoms of myelosuppression; Monitor LFTs
Blinatumomab BiTE(R) a bispecific T-cell engager IV	myelosuppresssion, cytokine release syndrome, neurological toxicity	Strictly follow product preparation and administration instructions; Monitor for neurologic complications and educate patient regarding signs/symptoms of same; Monitor for signs/ symptoms of infection and monitor for CRS
Clofarabine Antimetabolite IV	Myelosuppression; elevated LFTs; vomiting, nausea, diarrhea, abdominal pain, anorexia; elevated creatinine; headache; skin changes; tachycardia; limb pain	Monitor liver and renal function; Assess for skin changes and provide non-perfumed moisturizing lotion as needed; Monitor cardiac function; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/ symptoms of bleeding, and when to contact healthcare professional
Corticosteroids (dexamethasone, prednisone) Oral	Fatigue, thinning of skin, adrenal insufficiency, hyperglycemia, increased risk of infection, leukocytosis, bone thinning, osteoporosis, mood swings, personality changes, weight gain, decreased libido	Monitor for hyperglycemia/hypoglycemia; Educate patients on side effects including increased infection risk, signs/symptoms of infection and when to contact healthcare professional. Instruct not to abruptly stop taking corticosteroids
Cytarabine, High-dose (HiDAC) Antimetabolite IV, IT	Myelosuppression; headache; nausea/vomiting, stomatitis, diarrhea; skin rash; flu-like symptoms; alopecia; eye pain	Monitor renal function; monitor for signs of cerebellar toxicity and discontinue if present; discontinue agent if creatinine rises quickly; Provide antiemetics; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional
Dasatinib Tyrosine kinase inhibitor (TKI) Oral	Myelosuppression; diarrhea, nausea; headache; muscle/ bone pain; fever; skin rash; fluid retention, weight gain	Monitor for side effects and educate patient about same; Advise patient to contact healthcare professional for swelling, weight gain or increasing shortness of breath; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional
Daunorubicin Anthracycline IV	Pain at IV site; myelosuppression; nausea, vomiting, diarrhea; stomatitis; alopecia	Initiate recommended procedures to prevent drug extravasation; Educate patient on signs/symptoms of drug extravasation; Provide instructions on proper oral hygiene; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional

Drug/Class/ Route	Potential side effects	Management
Doxorubicin Anthracycline IV	Nausea, vomiting; fatigue; alopecia; oral ulcerations; sensitivity to sunlight; watery eyes, loss of fertility	Educate patients on side effects; Administration of pharmacologic interventions for prophylaxis of nausea/vomiting (benzodiazepines), for acute nausea/vomiting (5-HT3 receptor antagonists, dexamethasone, aprepitant, benzodiazepine); Hold ice chips in cheeks or suck on ice chips/ice cold water during administration; Referral to fertility specialist
Etoposide Plant alkaloid Oral	Neutropenia, thrombocytopenia; alopecia; nausea, vomiting, stomatitis, diarrhea; hypotension; radiation recall	Provide antiemetic as needed; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional
G-CSF/filgrastim Cytokine SQ	Joint, bone pain; elevated WBCs; pyrexia, elevated serum alkaline; headache	Assess and medicate for pain/discomfort
Idarubicin Anthracycline antitumor antibiotic IV	Vesicant; myelosuppression; nausea, vomiting, diarrhea, stomatitis; alopecia; heart rhythm abnormalities	Initiate recommended procedures to prevent drug extravasation; Educate patient on signs/symptoms of drug extravasation; Monitor total lifetime dose; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional
Imatinib Tyrosine kinase inhibitor (TKI) Oral	Myelosuppression; nausea/vomiting, diarrhea; headache; skin rash; muscle/joint pain; weight gain	This drug does not adequately penetrate the blood/brain barrier; Monitor CBC; Monitor for signs/symptoms of myelosuppression; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional; Provide antiemetics; Monitor hydration status if severe diarrhea/nausea/vomiting; Apply non-perfumed moisturizing lotion
Inotuzumab ozogamicin Monoclonal antibody and cytotoxic drug IV	Elevated LFTs; myelosuppression; nausea; GI distress; chills	Premedicate to prevent infusion-related reactions; Closely monitor liver enzymes; Monitor CBC; Monitor for signs/symptoms of myelosuppression; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional
L-asparaginase	Hypersensitivity reaction possible; pancreatitis, hemorrhage; thromboembolism; intracranial hemorrhage; cerebral thrombosis, ischemia or stroke; hyperglycemia; hepatotoxicity	Administration of anti-allergy premedication; Monitor for signs/symptoms of hypersensitivity reaction; Assess patient for neurologic changes; Educate patient on possible neurologic side effects and when to contact healthcare professional
Mercaptopurine Antimetabolite Oral	Myelosuppression; liver toxicity; nausea, vomiting, anorexia, diarrhea, stomatitis; loss of fertility; difficulty breathing	Assess CBC for alterations in hematologic status; Monitor LFTs; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional; Advise patient to consult a fertility specialist if desired; Educate patient to contact healthcare professional if experiencing difficulty breathing
Methotrexate Antimetabolite IV, IM, IT, Oral	Neutropenia, thrombocytopenia; stomatitis; vomiting; hepatotoxicity; azotemia (more common with high dose), hyperuricemia; neurotoxicity, pulmonary toxicity; renal dysfunction	Dose adjustments may be necessary in patients with hepatotoxicity or myelosuppression or in elderly patients; Monitor for signs/symptoms of infection and bleeding; Monitor renal function; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional

Drug/Class/ Route	Potential side effects	Management
Nelarabine Antimetabolite IV	Myelosuppression; nausea, diarrhea, constipation; cough; extreme fatigue; dizziness, peripheral neuropathy; shortness of breath; headache; swelling of feet or ankles, weight gain	Monitor for neurologic changes; Monitor for changes in weight; Provide education on conserving energy and measures to reduce fatigue; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional
Nilotinib Tyrosine kinase inhibitor (TKI) Oral	Myelosuppression; skin rash; headache	Assess CBC for alterations in hematologic status; Have patient apply non-perfumed skin moisturizer if needed; Advise patient to take acetaminophen if needed
Ponatinib Tyrosine kinase inhibitor (TKI) Oral	Hypertension; myelosuppression; hyperglycemia; hypophosphatemia; skin changes; elevated LFTs; abdominal pain, constipation, nausea; headache	Monitor BP and alert patient to signs/symptoms of hypertension; Monitor blood sugar and alert patient to signs/symptoms of hyperglycemia; Monitor LFTs and blood chemistry values; Provide medications and measures to reduce GI distress
Rituximab Monoclonal antibody IV	Fever, chills; weakness; nausea; headache; cough; cold symptoms	Administration of anti-allergy premedication; may cause temporary low BP; Advise patient to contact healthcare professional if any side effects become severe
Vincristine Plant alkaloid IV	Vesicant; alopecia; constipation; myelosuppression	Initiate recommended procedures to prevent drug extravasation; Educate patient on signs/symptoms of drug extravasation; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, and when to contact healthcare professional

BP, blood pressure; CBC, complete blood count; GI, gastrointestinal; LFT, liver function tests; IV, intravenous; SQ, subcutaneous; WBCs, white blood cells
Sources: NCCN 2019; http://chemocare.com/default.aspx; http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#a-content

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Appendix 1. Summary of Treatment Options in ALL

Treatment algorithm Chemotherapy includes induction therapy lasting 1–2 months, consolidation cycles (alternating) 6–8 months and maintenance therapy 2–2.5 years Prophylactic treatment to prevent CNS relapse is mandatory
Antibody therapy Anti-CD22 immunoconjugates directed against CD22 currently under investigation Anti-CD19; activation of patients' own T cells directed against CD19 Bispecific (CD3/CD19) blinatumomab under investigation, and already registered for adult R/R ALL, adult MRD+ ALL, pediatric R/R ALL Chimaeric antigen receptor-modified T cells directed against CD19 in early phase development
Targeted therapy with tyrosine kinase inhibitors in Ph+ ALL A tyrosine kinase inhibitor should be combined with chemotherapy in front-line therapy The tyrosine kinase inhibitor imatinib (400–800 mg/day) should be administered continuously, also post-HSCT Prolonged monitoring of BCR-ABL-1 MRD is recommended, as well as resistance mutation screening. In case of persisting MRD, increasing MRD level, or resistance mutation, switch to a second- or third-generation tyrosine kinase inhibitor
HSCT Allo HSCT in CR1 significantly improves OS and EFS in high-risk patients/MRD+ patients and is the best post-remission option for Ph+ ALL and MLL-rearranged ALL Conditioning regimens are age-adapted with full allo HSCT versus RIC for elderly patients or patients unfit for full conditioning The role of auto HSCT should be investigated for MRD-negative patients, in the setting of clinical trials All patients in CR ≥2 are candidates for allo HSCT
Options for relapsed/refractory ALL Full diagnostic work-up necessary to exclude/reveal clonal aberrations, and to provide bases for targeted therapies Different treatment for patients with short versus long first remission duration (>18/24 months) where re-induction is considered Treatment; there is no standard re-induction therapy established, new drugs most often used
ALL, acute lymphoblastic Leukemia; Ph, Philadelphia; MRD, measureable residual disease; CNS, central nervous system; Ph+, Philadelphia-positive; HSCT hematopoietic cell transplantation; allo HSCT, allogeneic HSCT; CR1, first complete remission; OS, overall survival; EFS, event-free survival; RIC, reduced-intensity conditioning; autoHSCT, autologous HSCT; CR ≥ 2, second or later complete remission Adapted from: Hoelzer 2016

Resources

Resources for Healthcare Professionals	
Leukemia Treatment Regimens: acute lymphoblastic Leukemia (ALL)	https://www.cancertherapyadvisor.com/home/cancer-topics/hematologic-cancers/Leukemia-treatment-regimens-acute-lymphoblastic-Leukemia-all/ https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/hematology/acute-lymphoblastic-Leukemia-2/
Detailed information on agents used in the treatment of cancer	http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#a-content
UK Medical Research Council. Updates on research activities in cancer	https://mrc.ukri.org/
Cancer Research UK. Information on cancer and cancer treatments	http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#a-content
UK Medical Research Council. Updates on research activities in cancer	https://mrc.ukri.org/
National Institute for Health and Care Excellence. Evidence-based guidance and updates on cancer treatment	https://www.cancerresearchuk.org/about-cancer
Deutsche Krebsgesellschaft: A listing of cancer centers in 6 European countries provided in English and German	https://www.oncomap.de/centerso
National Institute for Health and Care Excellence. Evidence-based guidance and updates on cancer treatment	https://www.nice.org.uk/
Information on research activities. In German	https://www.krebsgesellschaft.de/
National Comprehensive Cancer Network (NCCN)	https://www.cancer.gov/types/Leukemia/hp/adult-all-treatment-pdq https://www.Leukemia-net.org/content/patients/Leukemias/all/e4417/infoboxContent4418/ALL.pdf
Search information on National Cancer Institute (NCI) supported clinical trials	https://www.cancer.gov/about-cancer/treatment/clinical-trials/advanced-search
Resources for Patients and Families	
Information on chemotherapy agents including managing side effects. Sponsored by Cleveland Clinic, US	http://chemocare.com/default.aspx
Patient Power. Information on ALL and its treatment	https://patientpower.info/search/?center=&query=acute+lymphoblastic+Leukemia
Cancer Champions. Chemotherapy, Immunotherapy, Targeted Therapy. What's the difference?	https://cancer-champions.com/chemotherapy-immunotherapy-targeted-therapy-whats-the-difference/
Cancer Research UK. Information on cancer and cancer treatments targeted at patients	https://www.cancerresearchuk.org/about-cancer
Information on causes, symptoms, types and treatment of ALL from the European LeukemiaNet	https://www.Leukemia-net.org/content/patients/Leukemias/all/e4417/infoboxContent4418/ALL.pdf
Information on acute Leukemia/cancer. In Dutch and English	https://www.hovon.nl
Information on general cancer topics and research highlights. In German	https://www.krebsgesellschaft.de/

Quick Facts

- It is difficult to categorize problems experienced by patients with acute Leukemia as being related strictly to the disease or strictly to treatment
- Myelosuppression (manifested as anemia, thrombocytopenia and neutropenia) is a common and expected side effect of treatment as well as a consequence of acute Leukemia itself
- Mucositis, damage to the mucosal epithelium caused primarily by chemotherapy, can be extremely painful and lead to other problems such as weight loss, anorexia, dehydration and infection
- Supportive care measures should be tailored to meet individual patient needs based on factors such as age, performance status, extent of cytopenia, risks for infectious complications, disease status, and the specific agents used in treatment
- Caregivers are challenged to assimilate complex information, and as the home becomes the setting for continued care, they are challenged to develop skills to provide not only assistance with activities of daily living, but also with activities typically considered to be within the realm of nursing care or medical treatment

A. Introduction

B. Management of Early Crisis Conditions

1. Tumor lysis syndrome
2. Acute bleeding
3. Hyperleukocytosis
4. Cytokine release syndrome

C. Management of Side Effects of Disease and Treatment

1. Common problems
2. Febrile neutropenia

D. Considerations in Older Adults with Acute Leukemia

E. Management of the Patient undergoing Hematopoietic Cell Transplant

1. Common complications
2. Psychosocial issues
3. Longer term health-related issues

F. Psychosocial and Psychosexual Issues related to Acute Leukemia and its Treatment

1. Distress
2. Sexual activity
3. Fertility issues

G. Supportive Care

1. Pharmacological
2. Blood product transfusions
3. Nutrition, physical therapy, exercise
4. Care for the caregiver

H. Cancer Survivorship

I. End of Life Care

J. Educational Initiatives for Patients and Families

References

Resources

Introduction: Management of the Patient with Acute Leukemia

The diagnosis of acute Leukemia for patients and their families is a time filled with fear, uncertainty and many questions (Albrecht 2014). The patient is confronted with a sudden modification of lifestyle, which in turn has an impact on almost every dimension of daily life. The poor prognosis associated with acute Leukemia in adults can further increase distress concerning uncertainty about the future and fear of dying (Nørskov 2019); if left untreated, acute Leukemia can be fatal in a few weeks.

In contrast to other types of cancer, the trajectory of acute Leukemia involves an acute onset followed by an intensive treatment regimen, which is often complicated by a substantial symptom burden that can have profound effects on physical, emotional and psychological well-being and functioning (Chen 2018; Bryant 2015; Albrecht 2014; Papadopoulou 2013; Oliva 2011). In a study conducted to gain a better understanding of the symptom experience, significant improvements in global physical health, significant decreases in fatigue, anxiety, depression and sleep disturbances and significant increases in quality of life (QoL) were reported by patients at hospital discharge after induction therapy (Bryant 2018).

The treatment of acute Leukemia has dramatically changed in recent years now providing a significant improvement in response and survival rates in comparison to earlier treatment options. With few exceptions, it is difficult to categorize problems experienced by patients with acute Leukemia as being related strictly to the disease or strictly to treatment. Providing the supportive treatment necessitated by these problems is an essential part of the overall management of acute Leukemia.

Management of Early Crisis Conditions

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is a condition that occurs due to rapid destruction of tumor cells and is considered an oncologic metabolic emergency due to poor clinical outcome if it is unrecognized and untreated. The syndrome can occur spontaneously but primarily occurs with induction chemotherapy and is often evident within 12-72 hours after the initiation of cytotoxic therapy.

Clinical and laboratory manifestations of TLS:

- Hyperuricemia (uric acid > 8 mg/dL)
- Hyperphosphatemia (phosphorus > 4.5 mg/dL)
- Hyperkalemia (potassium > 6 mmol/L)
- Hypocalcemia (corrected calcium < 7 mg/dL, ionized Ca < 1.1)
- Marked elevation of lactate dehydrogenase (LDH)
- Acute kidney injury
- Cardiac arrhythmias
- Seizure/neuromuscular irritability

Adapted from: Emadi 2018

Symptoms are generally nonspecific and can include:

- Nausea with or without vomiting
- Lack of appetite and fatigue
- Dark urine, reduced urine output or flank pain
- Numbness, seizures or hallucinations
- Muscle cramps and spasms
- Heart palpitations

Standard TLS prophylaxis includes hydration with diuresis, and allopurinol administration or rasburicase treatment. Rasburicase is a genetically engineered recombinant form of urate oxidase enzyme and should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function (NCCN 2019). An advantage of rasburicase over allopurinol is that it provides rapid breakdown of serum uric acid, eliminating the need for urine alkalinization. Rasburicase, however, can cause severe hypersensitivity reactions including anaphylaxis in some patients.

Treatment of TLS includes

- IV fluids
- Allopurinol, especially rasburicase
- Correction of electrolyte imbalances

Acute bleeding

Patients with acute Leukemia are predisposed to bleeding and coagulation abnormalities. This risk stems from chemotherapy-induced thrombocytopenia, coagulation disorders or suppression of platelet production caused by severe infection.

Prophylactic treatment of bleeding may include:

- Platelet transfusions
- Mesna administration
- Tranexamic acid administration

Organ/location	Signs/symptoms of bleeding
Moderate risk of bleeding with platelet count < 20,000 – 50,000 x 10^9/L	
Skin	Petechiae
Oral cavity	Gingival bleeding
Genitourinary tract	Excessive menstrual flow, hematuria
Risk of severe bleeding with platelet count ≤ 20,000 x 10^9/L	
Intracranial bleed	Severe headache, stiff neck, vomiting, confusion
Pulmonary hemorrhage	Hemoptysis, breathing difficulty, cyanosis
Gastrointestinal hemorrhage	Hematochezia, dark/tar-like stools

Hyperleukocytosis (acute Leukemia blast crisis)

- Hyperleukocytosis is present at diagnosis in up to 20% of AML patients (Male 2018) but is relatively uncommon in ALL
- Pulmonary manifestations can range from mild respiratory distress to severe life-threatening hypoxia
- Neurologic symptoms can range from mild confusion to somnolence to stupor and coma; focal rather than global neurological deficits may be observable. Common signs/symptoms include: headache, blurred vision, visual loss, gait instability, tinnitus, cranial nerve deficits, retinal hemorrhage, papilledema and nuchal rigidity.
- Other clinical manifestations: acute myocardial infarction/arrhythmia; bowel ischemia/infarction; acute renal failure; limb ischemia; priapism

Ideally, hyperleukocytosis should be prevented through early administration of cytotoxic therapy, using a 7 + 3 induction regimen, for example. However, this is not always possible. Measures to manage hyperleukocytosis include:

1) cytotoxic chemotherapy: the most effective and beneficial treatment, but may not be immediately available if a diagnosis has not been confirmed
2) hydroxyurea: recommended if symptoms are mild
3) leukapheresis: limited to patients with probable or highly probable leukostasis symptoms (Male 2018; Rölling 2015)

Cytokine release syndrome

Cytokine release syndrome (CRS) can occur after treatment with some types of immunotherapy, such as monoclonal antibodies and CAR T cells. It is caused by a large, rapid release of cytokines into the bloodstream from immune cells affected by immunotherapy

Clinical manifestations of CRS:

- Fever, chills, fatigue, anorexia, myalgia, arthralgia
- Headache, altered mental status, delirium, aphasia, hallucinations, tremor, abnormal gait, seizures
- Skin rash
- Nausea, vomiting, diarrhea
- Tachypnea, hypoxemia, acute respiratory distress syndrome
- Tachycardia, hypotension, widened pulse pressure, cardiomyopathy
- Azotemia, elevated creatinine
- Transaminitis, hyperbilirubinemia

Adapted from: Emadi 2018

Management of CRS includes:

- Grade 1 (non-life-threatening symptoms) and Grade 2 (symptoms require moderate interventions) in the absence of comorbidities: Supportive care including treatment of febrile neutropenia; monitor fluid balance; administration of antipyretic medications; close monitoring of cardiac, renal and hepatic function
- Grade 2 (with comorbidities and in older patients), Grade 3 (symptoms require aggressive treatment), Grade 4 (presence of life-threatening symptoms): Aggressive supportive care plus tocilizumab with or without corticosteroids (Emadi 2018)

Management of Side Effects of Disease and Treatment

Management of Common Problems in Patients with Acute Leukemia

Myelosuppression, manifested as a reduction in red blood cells (causes anemia), neutrophils (neutropenia; causes an increased risk of infection) and platelets (thrombocytopenia; causes an increased risk of bleeding), is a common and expected side effect of the therapies used in acute Leukemia as well as a consequence of acute Leukemia itself. The severity of the side effects of anemia, neutropenia and thrombocytopenia will depend on how low the actual blood count of red blood cells, neutrophils and platelets, respectively, is and the duration of the lowered blood count.

Anemia and thrombocytopenia are generally treated using transfusion support (**Table 1**).

Fatigue is experienced by the majority of patients and can be a major cause of reduced physical functioning and lowered quality of life (Snowden 2011). The causes of fatigue are multifactorial and include treatable causes (anemia) as well as psychological and treatment-related causes (sedation medications). Cancer-related fatigue, in comparison to fatigue in healthy individuals, is less likely to be relieved by rest, is more distressing and differs in daily evolution profiles (Glaus 1996). Unfortunately, fatigue is often under-recognized by healthcare professionals. The use of a fatigue assessment tool/scale may aide in systematically and comprehensively collecting data on the patient's experience of fatigue.

Infection risk: A consequence of neutropenia and immunosuppression; risk varies according to the type/amount of chemotherapy received, conditioning regimen for hematopoietic cell transplant (HSCT) and other co-morbid conditions. Preventative measures are paramount to reducing infection risk and severity, but equally important are the early recognition of the signs and symptoms of infection and prompt initiation of appropriate treatment. Decisions regarding the use and choice of antibiotics to prevent and treat infections should be made on an individual and institution basis.

Thrombocytopenia: An abnormally low number of platelets, defined as < 100,000/mm^3. The risk of serious bleeding increases as the platelet level falls, and a risk of spontaneous bleeding is associated with a platelet count < 20,000/mm^3. Clinical trial evidence shows similar outcomes for patients who received prophylactic platelet transfusions at a level of 10,000/mm^3 rather than 20,000/mm^3.

Cerebellar toxicity: A dose-dependent secondary effect of cytarabine (ARA-C) that usually begins with cerebral effects (i.e., somnolence, confusion, disorientation, memory loss and cognitive dysfunction) and cerebellar signs such as dysarthria, ataxia, dysphagia and unsteady gait. Symptoms generally subside once cytarabine is stopped. Risk of occurrence increases in the presence of impaired renal function and in patients > 60 years.

Alopecia: Can occur after the administration of certain chemotherapy agents and is common after transplantation. It involves the loss of head and body hair and is a temporary condition; hair will grow back after chemotherapy is completed.

Gastrointestinal (GI) problems: Common GI symptoms in this setting include:

- oral mucositis
- esophagitis
- nausea
- vomiting
- diarrhea

Oral mucositis or stomatitis: Results from damage to the mucosal epithelium caused primarily by chemotherapy and can be extremely painful and lead to other problems such as weight loss, anorexia, dehydration and infection (Pallera 2004; Sonis 2004; Brown 2004). Lower incidences of grades 3 to 4 mucositis were reported in patients who sucked on ice chips or rinsed with ice-cold water during shorter infusions of chemotherapy (Svanberg 2010).

Peripheral neuropathy (PN): A neurologic dysfunction of peripheral, motor, sensory and autonomic neurons (EONS 2012a); associated with the use of vincristine and can be debilitating in some patients (Ludwig 2010). PN can impact QoL due to physical, social and psychological effects of unrelieved neuropathic pain (Tariman 2008). There are currently no effective medications to relieve neuropathic symptoms.

Pulmonary complications: Diffuse alveolar hemorrhage, characterized by the acute onset of alveolar infiltrates and hypoxemia, is a potentially life-threatening complication. Risk factors include older age, allogeneic HSCT and myeloablative conditioning (Majhail 2006). Treatment consists of corticosteroids and supportive care.

Table 1: Management of Common Problems in Patients with Acute Leukemia[a]

Problem	Clinical presentation	Management
Alopecia	Complete loss of hair	Teach patient about cause/duration of alopecia; provide psychosocial support; counsel regarding wig/head protection
Anemia	Fatigue; shortness of breath; chest pain on exertion; heart palpitations; pallor of skin/mucous membranes	Assess for signs/symptoms; provide education on expected occurrence of anemia; blood transfusions
Anorexia	Weight loss; taste changes; deterioration in general condition; fatigue; nausea, vomiting, diarrhea	Review medications as source of problem; provide oral nutritional supplements, IV hydration; small, frequent meals, calorie counts; weekly weight; nutrition consult; identify and correct underlying cause
Cerebellar toxicity	Somnolence, disorientation, cognitive dysfunction; dysphagia, unsteady gait	Perform neurologic assessment before each dose; discontinue cytarabine if signs/symptoms occur
Constipation	Symptoms can range from occasional/intermittent decrease in defecation to life-threatening consequences (obstruction)	Maintain a high fluid intake and high fiber diet if medically appropriate; increase physical activity; consider laxatives and stimulants
Diarrhea	Increased frequency of bowel movements, loose/watery/soft stools, abdominal cramps, dehydration, weight loss	Review medications as possible cause; evaluate electrolyte levels; administer antidiarrheal medication in the absence of GI infection; maintain/increase fluid intake; provide electrolyte replacement; obtain stool specimen for evaluation of enteric pathogens; provide nutritional supplements if indicated
Diffuse alveolar hemorrhage	Shortness of breath, hemoptysis, fever, chest pain, cough	Regularly assess for pulmonary complications; instruct patients to immediately contact healthcare provider if symptoms occur
Eye		Corticosteroid eye drops to both eyes daily for eye problems related to high-dose cytarabine
Fatigue	Decrease in energy; inability/difficulty performing activities of daily living; insomnia; not feeling rested after sleeping at night; generalized weakness	Encourage physical activity; evaluate nutritional intake; establish regular sleep/wake periods; advise patient to plan and prioritize daily activities; referral to physical therapy
Hemorrhagic cystitis	Hematuria; painful urination; urinary urgency/frequency; lower abdominal pain; nocturia; urinary incontinence	Assessment and recognition of common signs & symptoms; IV hydration; analgesics
Infection: prevention		Hand hygiene; contact precautions for resistant organisms; adherence to general infection control recommendations; Appropriate central venous catheter care; Safe handling and washing/thorough cooking of food; Administration of colony-stimulating factors (CSFs); antibiotic prophylaxis; antifungal prophylaxis; pneumocystis pneumonia prophylaxis[b]; antiviral prophylaxis
Infection: management	Fever, chills, myalgia, malaise, nausea, hypotension, hypoxia; sepsis (temperature > 38.5°C, tachycardia, muscle weakness, fatigue, confusion, drop in blood pressure)	Regularly monitor for signs & symptoms of infection (oral cavity, catheter exit site); administration of G-CSF until recovery of neutrophils; reduce drug dose or discontinue if neutrophil count <500/mm^3; infection prophylaxis with antibacterials, antivirals and antifungals; monitor for signs & symptoms of infection; if fever, initiate broad spectrum antibiotics, acetaminophen, hydration, symptom management
Nausea	Anorexia, weight loss; diminished skin turgor, dehydration; malnutrition if severe	Assess patterns of nausea; determine food intolerances; determine type of nausea (acute, delayed, anticipatory, breakthrough, refractory); may require IV fluids or nutritional support if severe

Problem	Clinical presentation	Management
Oral ulcerations (mucositis/stomatitis)	Soreness, erythema, ulcerations, of oral mucosa; difficulty swallowing	Oral care 5-6 times/day; administration of local/systemic analgesics; dietary modifications (moist/soft foods; avoidance of acidic, spicy, salty foods)
Pain	Patient report of new, or a change in existing pain	Routine assessment of pain at all stages of the disease; assess effect of analgesics and modify type of agent, titrate doses to effectiveness; local radiotherapy may provide pain relief; pain specialist consultation if necessary
Sepsis	Temperature ≥38°C; chills, shivers, discolored/clammy skin; "feeling unwell"; decreased urination; changes in mental status; tachycardia; tachypnea; hypotension	Frequent monitoring of VS and assessment for subtle changes in condition; oxygen therapy; blood cultures; IV antibiotics; IV hydration
Skin rash, dry skin	Symptoms generally self-limiting	Antihistamines for symptomatic treatment; assess for potential severe drug reactions
Thrombocytopenia	Mucosal/gastrointestinal bleeding; increased bruising, difficulty stopping bleeding; petechiae; oozing from catheter exit site	Obtain patient history of bleeding; initiate bleeding precautions; monitor CBC, differential and platelet count; examination of mucous membranes, sclerae, skin; neurologic assessment for symptoms of intracranial bleeding; reduce drug dose or discontinue if platelet count <25,000/mm^3
Vomiting	Mild (1 episode/24 hours) to more severe (6 episodes/24 hours); life-threatening consequences if severe	May be self-limiting; offer antiemetic; avoid noxious stimuli; may require IV fluids or nutritional support if severe

[a] Problems presented in this table can be related to acute Leukemia itself, the side effects of treatment and/or the side effects/complications of hematopoietic cell transplant (HSCT); [b] Should be administered to patients at risk for Pneumocystis pneumonia CBC, complete blood count; G-CSF, granulocyte colony stimulating factor; IV, intravenous; VS, vital signs;
References: EONS 2012b; Kenyon 2018; Majhail 2006; Snowden 2011; Tariman 2008; Wallhult 2018; Wilson 2018

Febrile neutropenia

Febrile neutropenia is defined as an oral temperature of > 38.3° C or two consecutive readings of > 38° C for 2 hours and an absolute neutrophil count (ANC) of < 0.5 x 10^9/L, or expected to fall below this level. Low neutrophil counts are a result of acute Leukemia, treatment with chemotherapeutic agents and the conditioning regimens used for HSCT. A break in mucosal integrity is a risk factor for developing bacteremia. Because the patient is neutropenic, typical signs and symptoms of infection (i.e., warmth and swelling), may not be present.

Table 2: Management of Febrile Neutropenia

Stage of Management	Activity
Preventative measures	Good handwashing/hygiene Avoidance of contact with persons with symptoms of infection Oral hygiene and skin care to maintain mucosal barrier Routine surveillance screening cultures for bacterial and/or fungal infections Antimicrobials for bacterial, viral and fungal pathogen prophylaxis[a] G-CSF administration
Assessment	Assess circulatory and respiratory function, gastrointestinal tract; skin; perineal region/genitourinary discharge; oropharynx; central nervous system
Treatment	Prompt initiation of broad-spectrum antibiotic coverage Blood cultures from peripheral blood and central lines; sputum and stool cultures Urinalysis; Chest radiograph/computed tomography Empiric antifungal treatment if fever is persistent over 4 days
HSCT	Viral prophylaxis may be maintained for longer periods and at higher doses Treatment required if patient is CMV-seropositive Due to high risk of encapsulated organism infection, TMP/SMX may be administered prophylactically

[a] Use should be limited to patients at high risk for febrile neutropenia; CMV, cytomegalovirus; G-CSF, granulocyte-colony stimulating factor; HSCT, hematopoietic cell transplantation.
Adopted from: Lucas 2018; Klastersky 2016

Decisions regarding the use and choice of antibiotics to prevent and treat infections should be made on an individual institution basis. Other prophylactic and treatment measures for neutropenia include:

- Initiation of empiric broad-spectrum antimicrobial therapy is an absolute necessity for febrile patients who are profoundly neutropenic
- White blood cell transfusions may be beneficial in selected patients with aplastic marrow and serious infections that do not respond to antibiotics
- Prophylactic oral antibiotics administered to patients with expected prolonged, profound granulocytopenia
- Serial surveillance cultures may be helpful in detecting the presence or acquisition of resistant organisms

Considerations in Older Adults

Because of the aggressive nature of most treatment regimens, older adults with acute Leukemia very often receive age-adopted treatment (see **Modules 3 and 4**). Older patients are more likely to experience poor health outcomes such as longer periods of neutropenia, increased rates of infection and longer hospital length of stay (Oran 2012). They are also less likely to achieve complete remission and remain relapse free compared to younger patients (Klepin 2014; Oliva 2011). Further, treatment regimens may change physical and functional abilities, health outcomes and overall QoL (Storey 2017).

Patient centered and holistic care are required to better manage co-morbidities and symptoms in older patients with acute Leukemia (Storey 2017). This approach may lead to improved physical function and an enhanced QoL in this population.

Management of the Patient undergoing Hematopoietic Cell Transplant

Hematopoietic stem cell transplant (HSCT) is an intensive treatment option for acute Leukemia. The complications of HSCT can be severe and have significant effects on patient outcomes such as physical functioning and QoL (**Table 3**) (Cohen 2012; Mosher 2011).

Table 3: Complications of Hematopoietic Cell Transplantation

Condition	Distinctive clinical and pathologic features
Acute GvHD	Rash with characteristic histologic features, ± fever, ± vascular leak, ± cholestatic hepatopathy with characteristic pathology; abdominal pain; diarrhea
Chronic GvHD	Infections, debilitating tissue injury leading to irreversible fibrosis; involves skin, eyes, oral cavity, liver, fascia
Hyperacute GvHD	GvHD with an onset before engraftment; Typical GvHD although often more abrupt and severe
Autologous GvHD	Predominantly skin involvement (rash with characteristic histologic features); ± diarrhea; symptoms may overlap with those of engraftment syndrome although vascular leak is less prominent
Hematopoietic graft rejection	Fever, vascular leak without engraftment, often with (host) count recovery

GvHD, graft versus host disease
Adapted from: Spitzer 2015

Psychosocial issues

In addition to clinical complications of HSCT, patients experience distressing physical and psychological symptoms such as severe fatigue, weakness, sleep disturbances, anxiety, lack of appetite, bowel problems and pain (Cohen 2012; Bevans 2008). Patients undergoing HSCT reported a steep deterioration in QoL and substantially worsening depression during hospitalization, which were correlated with baseline anxiety and depression (El-Jawahri 2014). Patients may experience disappointment and fear should the transplant fail and express feelings of anger, betrayal, grief, depression and hopelessness (Hutt 2018).

Longer-term health-related issues

While allo HSCT may cure the underlying acute Leukemia, there is a strong risk for late complications that can cause functional deficits and negatively affect QoL. Hence, screening and preventive practices for long-term survivors of HSCT are strongly recommended (see Majhail 2012). Plans of care and educational efforts should be directed at individual patient needs to help them and their caregivers better cope and manage the late effects of HSCT (Valenta 2017).

Psychosocial and Psychosexual Issues related to Acute Leukemia and its Treatment

Recognition of the person behind the cancer is a vital component of compassionate high-quality cancer care (Holland 2007). The feeling of a loss of autonomy is often experienced as patients find it increasingly difficult to maintain control over their new situation in light of the loss of personal control, independence and normality in everyday life (Papadopoulou 2013).

Healthcare professionals should take time to consider the profound changes that the diagnosis and treatment of acute Leukemia exert on QoL. According to a literature synthesis, the impact of acute Leukemia on QoL begins with the period after diagnosis until the end of treatment (Papadopoulou 2013). Hence, psychosocial interventions should begin at the time of diagnosis; timely attention to psychosocial issues may enhance long-term outcomes and improve QoL (Bugos 2015).

The impact of the diagnosis and treatment of acute Leukemia were found to increase the need for social support from healthcare professionals, social networks (family and friends) and other patients with acute Leukemia (Nørskov 2019). Further, social support can facilitate coping strategies (Nørskov 2019) and prevent and reduce the pathogenic psychological impact of acute Leukemia (Papadopoulou 2013). In fact, support from other patients can provide patients with a unique feeling of being understood that may not be attainable from well-meaning family, friends or healthcare team members.

Psychosocial issues with an effect on quality of life for patients with acute Leukemia	
Psychological	Coping Depression Anxiety Cognitive function Distress
Social	Missing life events Lengthy hospital visits/hospital admissions Financial burden Isolation from family, friends, pets
Adapted from: Corbitt 2018	

Distress

Distress is not a precise clinical term but can identify mood disorders including major depression and adjustment disorder. It is a term of usefulness to healthcare professionals working with cancer patients. Patients with acute Leukemia often experience distress at varying degrees during the disease trajectory. Consequences of untreated and unrecognized distress may result in poor satisfaction with medical care, prolonged hospitalization and a reduced QoL (Albrecht 2014; Carlson 2012). Distress for patients with Leukemia is multi-dimensional, quantifiable, subjective and temporal and can be influenced by factors such as education level, age and gender: that is, younger and female patients tend to be more prone to distress than older males (Albrecht 2017).

Recommendations to address distress and support psychosocial well-being:

- Assess for distress as soon as a diagnosis is established by simply asking the patient: "How is your distress on a scale of 0 to 10?". A score of ≥ 4 may indicate the need for further questions and possible referral to a psychosocial service; repeat assessment at key points in the care trajectory and at times of crisis such as remission, recurrence and disease progression
- Help patients to identify their old frames of reference to make sense of what they are currently experiencing
- Preserve patient autonomy and include them in decision-making to enhance a feeling of control and reduce distress
- Encourage spirituality for those patients for whom this is an important element in their life
- Work with patient to identify effective coping strategies
- Suggest antidepressants, which may be effective in reducing feelings of depression
- Implement psychoeducational interventions such as problem-solving therapy and counseling on techniques to improve communication
- Refer to support groups
- Suggest cognitive and behavioral therapy to manage anxiety and depression, possibly improve QoL
- Suggest activities such as relaxation techniques, meditation, yoga, regular exercise, massage, visualization and possibly dietary changes

Sources: Papadopoulou 2013; Carlson 2012; Cooke 2009; NCCN 1999

Sexual activity

Gender identity, sexual preference and types of sexual acts will influence the educational and informational needs of the patient. The content of patient education regarding sexual activity should take into consideration:

- Platelet counts
- Risk of infection
- Use of protection and barrier devices (condoms)
- Use of water-based lubricants
- Good hygiene for both partners
- Protection of partner from exposure to hazardous medications for 48 hours (Corbitt 2018)

Fertility

A discussion of fertility options should be conducted at the time of diagnosis.

Topics to be considered for discussion with female patients include:

- Providing education on options, refer to a fertility specialist early. Time for decision-making may be difficult as treatment for Leukemia must be started quickly
- Ideally, egg harvest should take place before initiation of treatment. The cost of egg and/or embryo preservation is often prohibitive, referral to a nonprofit assistance program might be appropriate
- The necessity to make decisions on future family planning may adversely impact QoL; patient may need to grieve the loss of natural family planning option (Corbitt 2018)

Topics to be considered for discussion with male patients include:

- Discuss options for cryopreservation of sperm, consider sperm donor if cryopreservation is not possible
- Consult patient/family on financial implications of sperm bank fees
- Stress of diagnosis and speedy decisions on fertility issues may cause undue burden and unsuccessful attempts at sperm collection
- Consider fertility risks of any chemotherapy agent to be used (Corbitt 2018)

Supportive Care

Supportive care consists of helping patients to manage both the symptoms of their condition and any side effects that may occur from treatment. Supportive care measures should be tailored to meet individual patient needs based on factors such as age, performance status, extent of cytopenia before and during therapy, risks for infectious complications, disease status, and the specific agents used in the Leukemia treatment regimen (NCCN 2019). Measures such as antiemetics, analgesics, blood product transfusions (red blood cell and platelet transfusions), tumor lysis prophylaxis, anti-infective prophylaxis, growth factor support as well as nutritional supplementation, relaxation techniques and emotional support may ease symptom burden and enhance quality of life.

Pharmaceuticals

- Antiemetics for prevention of nausea and vomiting: serotonin receptor antagonists, and/or neurokinin 1-receptor antagonists
- Analgesics for relief of pain/discomfort
- Regimens and agents to maintain bowel movement and prevent the occurrence of constipation (especially if the patient is receiving vincristine)
- Use of granulocyte colony-stimulating factor (G-CSF) when myelosuppressive therapy is administered

Blood product transfusions

Administration of blood products such as platelets and red blood cells (RBCs) may be necessary to support the patient during periods of myelosuppression.

- Leukocyte-depleted blood products should be used for transfusion support
- Irradiated blood products for patients receiving immunosuppressive therapy (i.e., fludarabine-based regimens, HSCT)
- HLA typing may be used to select platelet donors for patients who exhibit alloimmunization to HLA-specific antigens.

Nutrition, physical therapy, exercise

A number of factors can affect nutritional status and possibly lead to malnutrition:

- Intensive chemotherapy and other medications may affect the sense of taste and smell sometimes making favorite foods unappealing
- Oral mucositis can cause painful ingestion of food
- Nausea, vomiting and diarrhea may affect the desire to eat and/or the absorption of nutrients through the gut
- Anorexia or early satiety can reduce intake of foods and essential nutrients

Nutritional interventions:

- Physical assessment including a test of muscle function
- Nutritional assessment using a validated instrument and/or referral to a nutritionist
- Nutritional support in the form of oral nutritional supplements
- Consider enteral or parenteral support for >10% weight loss (NCCN 2019)

Studies on the timing, duration and intensity of physical exercise are either lacking or controversial. However, there is some evidence to support the benefit of physical activity on physical performance, QoL, symptom control and fatigue. Recommendations for physical activity are:

- Consultation with a physical therapist
- Moderate to vigorous intensity aerobic activity (as physical condition permits) to maintain and improve muscle mass and strength

Care for the caregiver

Both patients and caregivers need to adapt to a diagnosis of acute Leukemia, how it affects the individual patient and what changes in lifestyle will be necessary to increase the sense of being able to live with the disease. Caregivers are challenged to assimilate complex information, often very rapidly, and as the home becomes the setting for continued care, they are challenged to develop skills to provide not only assistance with activities of daily living, but also with activities typically considered to be within the realm of nursing care or medical treatment (**Table 4**). Families serve as the primary sources of support during treatment (Papadopoulou 2013). Caregivers may be relatives of the patient, friends, acquaintances or volunteers (Kurtin 2013) and their number and presence will vary depending on the patient's condition.

A caregiver plays an essential role in attaining and maintaining optimal outcomes throughout the disease process. While providing support, the caregiver also struggles with her or his own feelings about the diagnosis and the uncertainty about future events and how to cope with them. Healthcare professionals need to understand the role of the caregiver, the dynamics of the caregiver-patient relationship and causes of real and potential caregiver stress (Kurtin 2013).

Table 4: Key Elements of the Caregiver Role

Direct care activities	Monitor and report treatment side effects Procure and administer medications Make decisions on when to call a healthcare provider Make decisions on administering "as needed" medications Perform technical procedures (dressing changes, IV and pump care)
Indirect care activities	Serve as contact person for healthcare provider Serve as contact person for family, friends Serve as patient advocate Manage household Manage medical and insurance forms and bills Organize transportation
Emotional support	Balance medical expectations while maintaining hope Active listener Provide reassurance, emotional comfort

Adapted from: Kurtin 2013

Self-management in the home setting is becoming increasingly more prevalent as the length of time in hospital decreases. Hence, providing patients and their caregivers with clear instructions on recognizing and managing treatment side effects is important to optimize outcomes.

The demands of providing care produce changes in previous roles of caregivers, emotional well-being, social activities and employment. The level of care required by the patient strongly influences the caregiver's life, and can possibly negatively affect their state of health. Caregivers often require, but do not receive, the respite, healthcare, psychosocial and financial assistance they need to meet the many needs of the patient.

Providing care is a stressful undertaking; in terms of preventative care, assessment should be made of the

degree to which the caregiver's life and health may be negatively affected and recommendations provided on interventions to reduce any negative repercussions of caretaking (Bevans 2012).

Interventions to support caregivers:

- Individualize caregiver education
- Provide consistent and clear information, reinforce important concepts
- Provide written material
- Suggest maintaining a diary or log of treatments, blood counts, transfusions and side effects, the treatment administered and the outcome
- Encourage respite from caring for the patient and continuation of hobbies
- Encourage stress management practices such as walking and meditating
- Suggest hospital and community resources to support coping
- Provide criteria and procedure for emergency situations
- Encourage caregiver to seek help and/or assistance if needed

Cancer Survivorship

Cancer survivorship is defined as the period from the time of diagnosis until the end of life (NCI 2016). The essential components of survivorship care are:

- Prevention and detection of new cancers and recurrent cancer
- Surveillance for cancer spread, recurrence or second cancers
- Intervention for consequences of cancer and its treatment
- Coordination between specialists and primary care providers to ensure that all of the survivor's health needs are met (Hewitt 2006)

Cancer nurses are experts in managing many issues common to survivors of acute Leukemia and are pivotal in providing the essential components of survivorship care as listed above (Bugos 2015). To be successful, survivorship care requires a multidisciplinary effort and team approach. The overall goal of cancer survivorship is to empower survivors and their families (Morgan 2009).

End of Life Care

It is important that the interdisciplinary team recognize when a patient has advancing and untreatable disease to the point that death is likely to occur within the next several months. Discussions with patient and family regarding the right to accept or refuse further medical treatments, or even supportive care, should be initiated early and followed up with discussions on the patient's and carer's preferences for any type of future care and where this care should take place. Even when the patient is approaching the terminal stage and specific anti-cancer treatments have been withdrawn, blood and platelet transfusions can aid in maintaining quality of life by relieving exertional dyspnea and preventing bleeding (Snowden 2011). Timely referral to a palliative care team or hospice will allow for team members to become acquainted with the patient and family even if management of significant symptoms is not immediately needed.

Educational Initiatives for Patients and Families

There are several benefits to educating patients and their families. First, education may increase satisfaction, which can increase compliance with treatment. Providing accurate information can help to prepare patients for procedures and treatments thereby reducing anxiety and distress. Patients and their families are less distressed by side effects when they are aware of self-care strategies they can employ to ameliorate them (Ferrell 1995). Lastly, providing education strengthens the communication channels and trust between patients and providers of their care.

A number of individual variables influence the educational preferences of patients with cancer:

- Education and literacy
- Culture and religion
- Gender
- Age and developmental stage
- Past experience
- Health status
- Coping style
- Personality (Ream 2000)

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Resources

Resources for Healthcare Professionals	
National Institute for Health and Care Excellence. Evidence-based guidance and updates on cancer treatment	https://www.nice.org.uk/
Detailed information on agents used in the treatment of cancer	http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#a-content
Guidelines for survivorship care	National Comprehensive Cancer Network Guidelines. Survivorship. Available at: http://www.nccn.org/professionals/ physician_gls/pdf/survivorship.pdf. American Society of Clinical Oncology survivorship guidelines. Available at: http://www.asco.org/guidelines/survivorship
Management of side effects:	Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines for mucositis secondary to cancer therapy. http://www.ncbi.nlm.nih.gov/pubmed/24615748
Caring for the Caregiver. National Cancer Institute	www.cancer.gov/cancertopics/coping/caring-for-the-caregiver
Symptom Assessment Tools	
Grading System for Adverse Effects of Cancer Treatment	Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Seminars in Radiation Oncology 2003; 13: 176–181.
Grading System for Mucositis	World Health Organization (WHO) https://www.researchgate.net/figure/264009927_fig2_Table-1-World-Health-Organization-Oral-Mucositis-Assessment-Scale
Oral Mucositis Guidelines	European Oncology Nursing Society. Guidelines incorporate the latest developments in oral mucositis into standardized patient care. http://www.cancernurse.eu/documents/EONSClinicalGuidelinesSection4-en.pdf
Baseline Assessment for Peripheral Neuropathy	European Oncology Nursing Society. Peripheral Neuropathy: Improving symptom management in cancer care through evidence based practice. Euro PEP (Putting Evidence into Practice) Program. Available in several languages http://www.cancernurse.eu/documents/EONSPEPPeripheralNeuropathyEnglish.pdf
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Scale (neuropathic pain)	http://www.endoexperience.com/documents/Apx4_LANSS.pdf Bennett MI, Attal N, Backonja MM, et al. Using screening tools to identify neuropathic pain. Pain 2007: 127: 199–203

Resources

Symptom Assessment Tools	
Brief Pain Inventory (short form)	http://www.npcrc.org/files/news/briefpain_short.pdf
National Initiative on Pain Control Pain Assessment Scales	http://www.painedu.org/Downloads/NIPC/Pain%20Assessment%20Scales.pdf
Numeric Pain Intensity Scale	http:// www.partnersagainstpain.com/printouts/A7012AS2.pdf.
Impact of Cancer Scale	Zebrack BJ, Ganz PA, Bernaards CA, Petersen L, Abraham L. Assessing the impact of cancer: development of a new instrument for long-term survivors. Psychooncology. 2006; 15: 407-421
Concerns Checklist	National Cancer Survivorship Initiative- Concerns Checklist; http://www.ncsi.org.uk/wp-content/uploads/MAC13689_Identifyingconcerns_Pad_v3.pdf
Resources for Patients and Families	
Prevention of Infection	American Cancer Society: http://bit.ly/2Cr6a4j Center for Disease Control and Prevention: http://bit.ly/2icj1fI National Comprehensive Cancer Network: http://bit.ly/2AoFKhP
Information on chemotherapy agents including managing side effects. Sponsored by Cleveland Clinic, US	http://chemocare.com/default.aspx
Cancer Champions. Chemotherapy, Immunotherapy, Targeted Therapy. What's the difference?	https://cancer-champions.com/chemotherapy-immunotherapy-targeted-therapy-whats-the-difference/
Taking Care of Yourself	www.curetoday.com/index.cfm/fuseaction/article.show/id/2/article_id/185
National Coalition for Cancer Survivorship	www.canceradvocacy.org
Know AML A global AML awareness initiative	https://know-aml.com/en (Also available in French, Italian, German and Spanish)
OncoLink OncoLife Survivorship Care Plan	www.oncolink.com/oncolife
Stupid Cancer	www.stupidcancer.org
Information on acute Leukemia/cancer. In Dutch and English	https://www.hovon.nl
Information on general cancer topics and research highlights. In German	https://www.krebsgesellschaft.de/
Distress NCCN Guidelines for Patients	https://www.nccn.org/patients/guidelines/distress/files/assets/basic-html/page-1.html#
Fatigue Tired of Cancer: an "untire" app to help cancer patients and survivors cope with extreme fatigue	https://tiredofcancerapp.com/

Glossary of Terms*

Term	Definition
Acute Leukemia	A pathophysiologic proliferation of immature bone marrow-derived cells (blasts) that may also involve peripheral blood or solid organs
Allogeneic hematopoietic cell transplantation	A procedure in which stem cells from a genetically matched, donor are transfused into the recipient
Alopecia	The lack or loss of hair from areas of the body where hair is usually found. Alopecia can be a side effect of chemotherapy and radiation therapy
Anemia	A condition in which the hemoglobin level and usually the number of red blood cells (erythrocytes) are below normal range
Autologous stem cell transplantation	A procedure in which stem cells are harvested, stored and later infused into the same person
Chimeric antigen receptor therapy (CAR T cells)	This therapy relies on the genetic manipulation of a patients' T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19
Cerebellar toxicity	Dose-dependent secondary effect of cytarabine; high doses are linked to the greatest risk of developing this syndrome
Complete response (CR)	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission
Cytochemistry	The biochemistry of cells, especially that of the macromolecules responsible for cell structure and function; also describes a process of identification of the biochemical content of cells
Cytogenetics	The study of the structure and function of chromosomes
Cytokine Release Syndrome (CRS)	Cytokine release syndrome (CRS) is a form of systemic inflammatory response syndrome (SIRS) that can be triggered by a variety of factors such as infections and certain drugs. It refers to cytokine storm syndromes (CSS) and occurs when large numbers of white blood cells are activated and release inflammatory cytokines, which in turn activate yet more white blood cells. CRS is also an adverse effect of some monoclonal antibody medications, as well as adoptive T-cell therapies. When occurring as a result of a medication, it is also known as an infusion reaction
Cytomorphology	The morphology (form) of cells
Diffuse alveolar hemorrhage	A life-threatening and medical emergency; can be caused by numerous disorders and presents with hemoptysis, anemia and diffuse alveolar infiltrates
Disease-free survival	A concept used to describe the period after successful treatment during which there are no signs and symptoms of the disease
Disseminated intravascular coagulation	A condition in which small blood clots develop throughout the bloodstream, blocking small blood vessels. The increased clotting depletes the platelets and clotting factors needed to control bleeding; leads to excessive bleeding
Erythropoiesis-stimulating agent	A drug that stimulates the bone marrow to produce red blood cells (erythrocytes)
Extramedullary sites	Situated or occurring outside the spinal cord or the medulla oblongata
Fatigue	Extreme tiredness despite getting enough sleep; interferes with the ability to carry out daily activities
Fluorescent in situ hybridization (FISH)	A test using special fluorescent dyes that attach to specific genes or parts of particular chromosomes. FISH identifies most chromosome changes (such as translocations) that are visible under a microscope in standard cytogenetic tests as well as some changes too small to be seen with usual cytogenetic testing. Can be used on peripheral blood or bone marrow or from tissues such as lymph node samples
Flow cytometry	A laboratory method used to detect, identify and count specific cells based on physical characteristics and/or markers called antigens on the cell surface or within cells that are unique to that cell type

Term	Definition
Genomic characterization Genetic profiling	A laboratory method used to evaluate genes and the way genes interact with each other and with the environment. Can be useful in identifying genetic predisposition to certain diseases or response to treatment
Genomics	The study of the complete set of DNA
Granulocyte colony-stimulating factor (G-CSF)	Glycoproteins that promote production of white blood cells (mainly granulocytes such as neutrophils), in response to infection; stimulates stem cells in the bone marrow to produce more of the particular white blood cells
Haplo	Simple; single
Hematopoietic stem cells	The stem cells that give rise to other blood cells in a process called hematopoiesis
Hematopoietic stem cell transplantation (HSCT)	Hematopoietic stem cell transplantation (HSCT) is the transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood. It may be autologous (the patient's own stem cells are used), allogeneic (the stem cells come from a donor) or syngeneic (from an identical twin).
Hemorrhagic cystitis	Inflammation of the bladder defined by lower urinary tract symptoms that can include dysuria, hematuria and hemorrhage. Can be caused by cyclophosphamide, ifosfamide and radiation therapy
Human leukocyte antigen (HLA)	A gene complex encoding the major histocompatibility complex (MHC) proteins in humans. These cell-surface proteins are responsible for the regulation of the immune system
Immunconjugate therapy	Treatment that uses an immune substance, such as a monoclonal antibody, that is chemically linked to a cell-killing substance such as a toxin, radioisotope or drug. The immune substance targets certain types of cells and the linked substance kills the targeted cells without harming other cells
Immunoconjugate	Classification of Leukemia cells according to the substances (antigens) on their surfaces. Leukemia cells can have different antigens depending on the type of cell in which the Leukemia originated and the maturity of the cell
Immunosuppression	Suppression of the immune system and the ability to fight infections and other disease
Immunosuppressive therapy	Deliberate drug- or radiation-induced suppression of the immune system often in preparation for hematopoietic stem cell transplantation
Karyotype	Analysis of the chromosomes of the leukemic cells
Leukocyte	A blood cell produced in the bone marrow and found in peripheral blood and lymph tissue; cells are part of the immune system. Types are granulocytes, monocytes and lymphocytes
Leukocytosis	An increase in the number of white cells in the blood, especially during an infection
Leukopenia	Decrease in the number of leukocytes, which are the body's primary defense against infection
Lymphoblast	A modified naïve lymphocyte with altered cell morphology. Refers to immature cells, which typically differentiate to form mature lymphocytes. In acute lymphoblastic Leukemia (ALL) this term refers to malignant leukemic cells, precursors of the lymphocytes which multiply uncontrollably
Lymphoid cell	Any of the cells responsible for the production of immunity mediated by cells or antibodies and including lymphocytes, lymphoblasts and plasma cells
Measureable/minimal residual disease (MRD)	Disease remaining after implementation of treatment, at such a low level that it can not be detected by classic techniques such as microscopy
Monoclonal antibody	A type of protein made in the laboratory that can bind to substances in the body; developed to bind to only one substance
Mucositis	A complication of some chemotherapy/radiation therapy in which the lining of the digestive system becomes inflamed. Often seen as sores in the mouth

Term	Definition
Myeloablative therapy	High-dose (most often) chemotherapy that kills cells in the bone marrow, including cancer cells. It lowers the number of normal blood-forming cells in the bone marrow and can cause severe side effects
Myeloblast	A unipotent stem cell which differentiates into the effectors of the granulocyte series; found in the bone marrow
Myelosuppression	A condition in which bone marrow activity is decreased, resulting in fewer erythrocytes, platelets and neutrophils.
Nadir	The lowest point. May refer, for example, to the lowest blood count after chemotherapy or the lowest concentration of a drug in the body
Natural killer cells	A lymphocytes able to bind to certain tumor cells and virus-infected cells without the stimulation of antigens, and destroy them by the insertion of granules containing perforin
Neoplastic cells	Cancer/malignant cells
Neutropenia	Decrease in the number of granulocytes, which are white blood cells, and provide the primary defense against infection
Oncogene	A gene that is a mutated (changed) form of a gene involved in normal cell growth. Oncogenes may cause the growth of cancer cells. Mutations in genes that become oncogenes can be inherited or caused by being exposed to substances in the environment that cause cancer
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment that patients diagnosed with the disease are still alive; used in clinical trials to measure the efficacy of a treatment
Pancytopenia	Reduction in the number of erythrocytes, platelets and granulocytes
Phenotype	The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment
Polymerase chain reaction (PCR)	A laboratory technique used to make multiple copies of a segment of DNA; very precise and can be used to amplify, or copy, a specific DNA target from a mixture of DNA molecules
Progenitor cells	A biological cell that, like a stem cell, has a tendency to differentiate into a specific type of cell, but is already more specific than a stem cell and is pushed to differentiate into its "target" cell
Quality of Life (QoL)	An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns
Residual disease	Quantity of malignant cells remaining after the administration of a treatment. To determine this, very different specific laboratory techniques may be used
Stomatitis	Inflammation or irritation of the mucous membranes in the mouth
Thrombocytopenia	A condition in which there is a lower-than-normal number of platelets in the blood; may cause easy bruising and bleeding from wounds or bleeding in mucous membranes
Tumor lysis syndrome (TLS)	A condition that occurs when a large number of cancer cells die within a short period, releasing their contents in to the blood
Tumor suppressor gene	A type of gene that makes a protein called a tumor suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer. Also called antigene

*The terms listed in this glossary are not necessarily specific to acute Leukemia. Some terms refer to general concepts in the diagnosis, treatment and management of cancers and other diseases or conditions.

Notes

Notes

HNHCP
Haematology Nurses & Healthcare Professionals Group

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