Cancer Association of South Africa (CANSA)

Research • Educate • Support

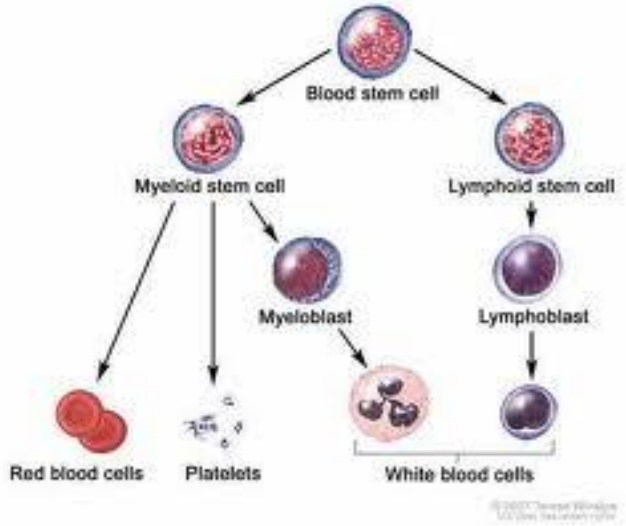
Fact Sheet on Adult Acute Myeloid Leukaemia (AML)

Introduction

The word *leukaemia* literally means 'white blood' and is used to describe a variety of cancers that begin in the blood-forming cells (lymphocytes) of the bone marrow.

Leukaemias are divided into two major types:

- Acute Leukaemia which progresses quickly with many immature white cells
- Chronic Leukaemia which progresses more slowly and has more mature white cells



[Picture Credit: Blood Cell Formation]

Both leukaemia and lymphomas (Hodgkin's disease and non-Hodgkin's lymphomas) are cancers of lymphocytes. The difference is that leukaemia starts in the bone marrow while lymphomas originate in lymph nodes and then spread to the bone marrow or other organs.

White blood cells (*leukocytes*) evolve from immature cells referred to as *blasts*. Malignancy of these blast cells is the source of leukaemias, which generally progress as follows:

- Normally, blasts constitute 5% or less of healthy bone marrow. In leukaemia, however, these blasts remain immature and multiply continuously but fail to mature properly, eventually constituting between 30 - 100% of the bone marrow.

- In time, these malignant blast cells fill up the bone marrow and prevent production of healthy red cells, platelets and mature white cells (leukocytes).

- Malignant blasts spill out of the marrow into the bloodstream and lymph system and can travel to the brain and spinal cord (the central nervous system). Some blasts are called *lymphoblasts* (which normally become mature cells called *lymphocytes*) and others are called *myeloblasts* (which mature to *myeloid* cells).

(University of Maryland Medical Center).

Blood consists of three types of cells and cell fragments floating in a liquid called plasma. These cellular components are:

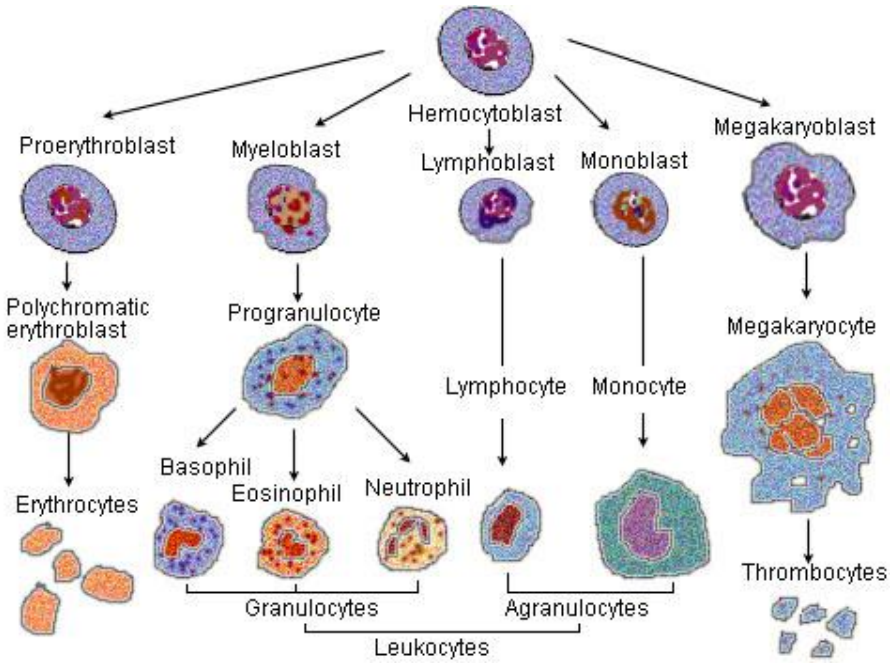
- **Red Blood Cells** (‘erythrocytes’, ‘RBCs’) - oxygen-carrying cells
- **White Blood Cells** (‘leukocytes’, ‘WBCs’) - cells that help make up the body's immune system
- **Platelets** (‘thrombocytes’) - fragments of cells that play an important role in formation of blood clots

The total number of white blood cells normally ranges from 4 million to 11 million cells per millilitre of blood. Leukaemias are a group of diseases characterised by *increased numbers of white cells* in the blood and bone marrow.
(Cancerquerst).

Adult Acute Myeloid Leukaemia (AML)
Adult Acute Myeloid Leukaemia (AML) is the most common type of acute leukaemia diagnosed in adults.

Different leukaemias are diagnosed according to the type of white blood cell affected and the speed with which the cancer progresses. AML is an acute leukaemia meaning that it is more aggressive and progresses quickly. It affects a type of white blood cells called myeloid cells (granulocytes and monocytes).

[Picture Credit: White Blood Cells]



White blood cells are made in the bone marrow – the soft tissue in the middle of our bones where all our blood cells are made. Mother cells, called stem cells, reside here and make every type of blood cell that we need. Stem cells constantly produce new blood cells to replace old and damaged ones. New cells only leave the bone marrow once they have fully matured. This is a controlled process which ensures that just the right amount of each blood cell is present in the body.

When someone has leukaemia, control of blood cell production breaks down. The stem cells make very large numbers of immature blood cells. In the case of AML these are abnormal, or cancerous, myeloid cells. These never mature into proper white blood cells, vital to a healthy immune system, and so people with AML have an increased risk of infection.

The cancer cells cluster in the bone marrow and prevent other important blood cells from being made. Most of the problems of leukaemia are caused by the lack of normal cells in the blood, rather than the leukaemia cells themselves.
(Leukaemia and Lymphoma Research).

Acute Promyelocytic Leukaemia (APL)
Acute promyelocytic leukaemia (APL) is a form of cancer that affects the stem cells which produce myeloid blood cells in the bone marrow. Please refer to the separate Fact Sheet on Acute Promyelocytic Leukaemia.
(Leukaemia and Lymphoma Research).

Incidence of Adult Acute Myeloid Leukaemia (AML)
In providing the incidence figures of Leukaemia in South Africa, The National Cancer Registry (2012) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia.

According to the National Cancer Registry (2012) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	380	1:502	1,03%
Asian males	11	1:666	1,34%
Black males	201	1:762	1,73%
Coloured males	42	1:452	0,97%
White males	126	1:232	0,63%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	285	1:955	0,76%
Asian females	5	1:1 777	0,47%
Black females	160	1:1 409	0,97%
Coloured females	49	1:440	1,17%
White females	72	1:480	0,45%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	88	29	38	42	50	54	54	20
Asian males	3	1	0	0	1	2	2	2
Black males	67	21	25	20	20	23	13	3
Coloured males	6	2	5	1	8	6	8	4
White males	12	5	6	18	18	23	30	11

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	63	19	24	34	42	37	31	20
Asian females	0	1	1	2	1	0	0	0
Black females	40	18	27	16	22	11	12	6
Coloured females	10	4	3	3	5	13	5	5
White females	12	3	1	6	14	12	14	9

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes of Adult Acute Myeloid Leukaemia (AML)

In most cases the causes of AML remain largely unknown but it is thought to result from damage to one or more of the genes that normally control blood cell development. Research is going on all the time into finding possible causes of this damage. Certain factors have been identified that may put some people at an increased risk.

These include exposure to:

- very high doses of radiation, either accidentally (nuclear accident) or therapeutically (to treat other cancers),
- industrial chemicals like benzene over a long period, certain types of chemotherapy to treat other cancers
- cancer-causing substances in tobacco smoke.

Some people with pre-existing blood disorders like certain myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), or certain genetic disorders like Down's Syndrome, Bloom Syndrome and Fanconi's anaemia may have a higher than average risk of developing AML.
(Leukaemia Foundation).

Risk Factors for Adult Acute Myeloid Leukaemia (AML)

Anything that increases one's risk of getting a disease is called a risk factor. Having a risk factor does not mean that one will get cancer; not having risk factors does not mean that one will not get cancer.

Possible risk factors for AML include the following:

- Being male.
- Smoking, especially after age 60.
- Having had treatment with chemotherapy or radiation therapy in the past.
- Having had treatment for childhood acute lymphoblastic leukaemia (ALL) in the past.
- Being exposed to radiation from an atomic bomb or to the chemical benzene.
- Having a history of a blood disorder such as myelodysplastic syndrome.

(University of Michigan Health System).

Signs and Symptoms of Adult Acute Myeloid Leukaemia (AML)

Typically AML comes on suddenly, within days or weeks. Less often, a patient has been ill for a few months or may have a prior history of Myelodysplastic Syndrome.

AML makes people sick primarily by interfering with normal bone marrow function. The leukaemia cells replace and crowd out the normal cells of the bone marrow, thereby causing

low blood cell counts. This insufficient number of red blood cells results in a condition called anaemia, which causes a person to be tired and pale. Lack of platelets can make one more susceptible to bleeding and bruising, especially in the skin, nose and gums. Lowered levels of normal white blood cells increase the risk of infection.

Although infections can be of any type, typical symptoms include:

- Fever
- Lethargy and fatigue
- Pale skin
- Easy bruising
- Swollen lymph nodes
- Swollen gums
- Unusual bleeding, such as frequent nosebleeds and bleeding from the gums
- Bone pain
- Runny nose
- Cough
- Chest pain or shortness of breath
- Pain with urinating
- Abdominal discomfort due to swollen liver or spleen
- Diarrhoea, occasionally
- Infections of the bloodstream, called sepsis, and pneumonia are the most dangerous

(UCSF Medical Center; Mayo Clinic; Leukaemia Foundation).

Diagnosis of Adult Acute Myeloid Leukaemia (AML)

Tests that examine the blood and bone marrow are used to detect (find) and diagnose adult AML.

The following tests and procedures may be used:

- Physical examination and history: An examination of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments is also usually taken

- Complete blood count (CBC): A procedure in which a sample of blood is drawn and checked for the following:
    - The number of red blood cells, white blood cells, and platelets
    - The amount of haemoglobin (the protein that carries oxygen) in the red blood cells
    - The portion of the sample made up of red blood cells

  Blood is collected by inserting a needle into a vein and allowing the blood to flow into a tube. The blood sample is sent to the laboratory and the red blood cells, white blood cells, and platelets are counted. The CBC is used to test for, diagnose, and monitor many different conditions

- Peripheral blood smear: A procedure in which a sample of blood is checked for blast cells, the number and kinds of white blood cells, the number of platelets, and changes in the shape of blood cells

- Bone marrow aspiration and biopsy: The removal of bone marrow, blood, and a small piece of bone by inserting a hollow needle into the hipbone or breastbone. A pathologist views the bone marrow, blood, and bone under a microscope to look for signs of cancer

  Bone marrow aspiration and biopsy. After a small area of skin is numbed, a Jamshidi needle (a long, hollow needle) is inserted into the patient's hip bone. Samples of blood, bone, and bone marrow are removed for examination under a microscope

- Cytogenetic analysis: A laboratory test in which the cells in a sample of blood or bone marrow are viewed under a microscope to look for certain changes in the chromosomes. Other tests, such as fluorescence in situ hybridization (FISH), may also be done to look for certain changes in the chromosomes

- Immunophenotyping: A process used to identify cells, based on the types of antigens or markers on the surface of the cell. This process is used to diagnose the subtype of AML by comparing the cancer cells to normal cells of the immune system. For example, a cytochemistry study may test the cells in a sample of tissue using chemicals (dyes) to look for certain changes in the sample. A chemical may cause a colour change in one type of leukaemia cell but not in another type of leukaemia cell

- Reverse transcription–polymerase chain reaction test (RT–PCR): A laboratory test in which cells in a sample of tissue are studied using chemicals to look for certain changes in the structure or function of genes. This test is used to diagnose certain types of AML including acute promyelocytic leukaemia (APL)

(University of Michigan Health Center).

Classification of Acute Myeloid Leukaemia (AML)

There are 2 staging systems that are commonly used during diagnosis of acute myeloid leukaemia (AML). The French-American-British (FAB) classification system is based on morphology to define specific immunotypes. The World Health Organization (WHO) classification reviews chromosome translocations and evidence of dysplasia.

FAB classification of AML

FAB subtype	Name	Adult AML patients (%)
M0	Undifferentiated acute myeloblastic leukaemia	5%
M1	Acute myeloblastic leukaemia with minimal maturation	15%
M2	Acute myeloblastic leukaemia with maturation	25%
M3	Acute promyelocytic leukaemia	10%
M4	Acute myelomonocytic leukaemia	20%
M4eos	Acute myelomonocytic leukaemia with eosinophilia	5%
M5	Acute monocytic leukaemia	10%
M6	Acute erythroid leukaemia	5%
M7	Acute megakaryocytic leukaemia	5%

WHO classification of AML and related neoplasms

AML with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBEB-MYH11*
- Acute promyelocytic leukaemia (APL) with t(15;17)(q22;q12); *PML-RARA*
- AML with t(9;11)(p22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- Provisional entity: AML with mutated NPM1
- Provisional entity: AML with mutated CEBPA

AML with myelodysplasia-related change

Therapy-related myeloid neoplasms

AML, not otherwise specified:

- Undifferentiated AML (M0)
- AML with minimal differentiation (M1)
- AML without maturation (M2)
- AML with maturation (M2)
- Acute myelomonocytic leukaemia (M3)
- Acute monoblastic/monocytic leukaemia (M4)
- Acute erythroid leukaemia (M5)
- Pure erythroid leukaemia (M6)
- Erythroleukaemia, erythroid/myeloid (M6)
- Acute megakaryoblastic leukaemia (M7)
- Acute basophilic leukaemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome:

- Transient abnormal myelopoiesis
- Myeloid leukaemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm
(Medscape).

Treatment of Adult Acute Myeloid Leukaemia (AML)

The usual treatment of AML is divided into two phases: induction of remission and post-remission therapy.

Induction therapy - the initial phase of treatment is referred to as remission induction or 'induction' therapy. Induction therapy is given with the goal of decreasing the number of leukaemia cells to an undetectable level and restoring the production of normal blood cells.

Most of the cells in one's body divide and multiply slowly and are not affected by chemotherapy. However, certain cells, such as those in the bone marrow (where the blood cells are produced), the hair follicles, and the cells lining the gastrointestinal (GI) tract are multiplying rapidly. As a result, chemotherapy is most likely to cause side effects such as

anaemia (lowered red blood cell count), susceptibility to infection (lowered white blood cell count or low haemoglobin level) and bleeding (lowered platelet count). Other side effects include temporary loss of hair, sores in the mouth, upset stomach, and diarrhoea.

The most common remission induction regimens include cytarabine, given continuously for seven days through an intravenous (IV) line.

An anthracycline drug, such as daunorubicin or idarubicin, is also given in a single IV dose for the first three days of treatment. This is sometimes known as the '7+3' regimen. These drugs kill AML cells over the first 7 to 14 days; it then takes the normal bone marrow about 14 days to recover and produce normal blood cells again.

This phase of treatment takes approximately four weeks and is almost always performed while the patient stays in the hospital. The induction phase usually consists of one or two cycles. A cycle of chemotherapy refers to the time it takes to give the drugs and the time required for the body to recover.

Induction therapy frequently results in a complete remission of the AML, meaning that there are no visible leukaemia cells in the blood or bone marrow when examined under a microscope and that the bone marrow is functioning normally. However, such remissions are usually short-lived unless additional, post-remission therapy is given.

Complete remission — the first goal of AML treatment is to achieve a complete remission. Complete remission means that there is no visible evidence of leukaemia cells in the blood or bone marrow and the bone marrow is functioning normally. A bone marrow biopsy and blood testing are done to determine when/if this occurs.

Post-remission therapy - is given with the intention of killing leukaemia cells that can remain in the bone marrow or blood, but are undetectable under the microscope.

There are three basic treatment choices for post-remission therapy: additional chemotherapy, stem cell transplantation from a donor (allogeneic hematopoietic stem cell transplantation), or stem cell transplantation using your own stem cells (autologous hematopoietic stem cell transplantation).

The 'best' post-remission treatment depends upon several factors, including how aggressive or resistant to treatment the AML is:

- People with favourable risk disease are usually advised to continue with chemotherapy. Many of these patients are cured in this way

- People with unfavourable risk disease are usually advised to have an allogeneic stem cell transplantation

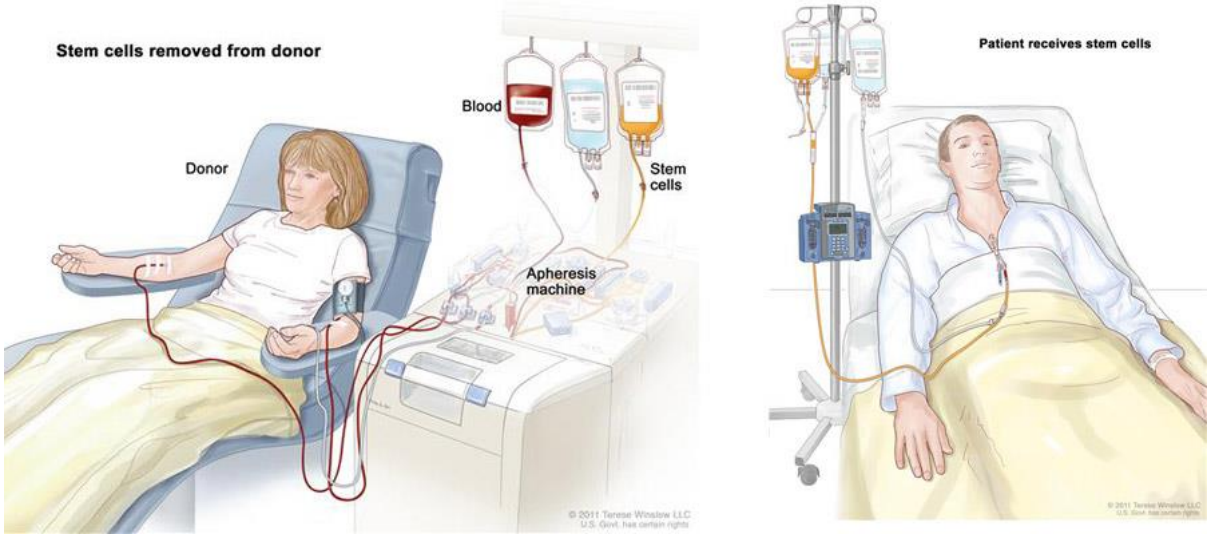
- The best treatment for intermediate risk disease is not clear; participation in a clinical trial is recommended, when possible

Additional chemotherapy — chemotherapy given after remission is called remission consolidation or post-remission chemotherapy, and often includes high-dose cytarabine.

Consolidation chemotherapy is usually given in the hospital monthly over several days. Consolidation chemotherapy is given for approximately three to four months.

Stem cell transplantation — stem cell transplantation, also called bone marrow transplantation or haematopoietic stem cell transplantation, is a treatment in which the patient is given very high doses of chemotherapy or total body irradiation (TBI).

This treatment is intended to kill cancer cells, but it also destroys all normal cells developing in the bone marrow. This means that the body's normal source of critical blood components (i.e., the bone marrow) is no longer functional.



[Picture Credit: Stem Cell Transplant]

After the treatment, the patient must have a healthy supply of young blood cells (called stem cells) re-introduced, or transplanted using transfusion. The transplanted cells then re-establish the blood cell production process in the bone marrow. The new stem cells also generate a new immune system.

Stem cell transplantation is not recommended for all patients with AML. Serious, and sometimes even fatal, complications occur more commonly after stem cell transplantation than with chemotherapy. In certain groups of people, there is no clear benefit of stem cell transplantation over chemotherapy. However, transplantation may be appropriate in some people, such as those with more aggressive forms of AML, those who have had a relapse following remission, and those who do not achieve remission after initial induction therapy.

There are two main types of stem cell transplantation: allogeneic and autologous.

Allogeneic transplantation - uses stem cells from a healthy donor, ideally a sibling with a similar genetic makeup (called an HLA-matched related donor; MRD). The HLA genes are inherited from both parents and govern one's immune system. If the patient does not have a sibling with similar genetic characteristics, an unrelated person with a similar genetic makeup may be used (called a matched unrelated donor; MUD). Other possibilities include the use of a sibling with partially similar genetic characteristics (partially matched family member donor) or cord blood stem cells collected from a new born baby's umbilical cord.

Allogeneic transplantation treats AML in two ways. First, high doses of chemotherapy or radiation are given immediately before the transplant, which kills the leukaemia cells present in the blood and bone marrow that might be resistant to lower doses of chemotherapy. Second, when cells from another person are injected, the donor stem cells develop into immune cells that can identify the leukaemia cells as foreign and launch an immune attack that helps destroy any remaining leukaemia cells. This is called the 'graft versus leukaemia' or 'graft versus tumour' effect.

Unfortunately, this response can lead to a complication called 'graft versus host disease', in which the immune response includes an attack on the body's own healthy organs. Symptoms can include severe skin rash, diarrhoea, liver damage, and other problems. Still, allogeneic transplantation is generally preferred over autologous transplantation in people with AML.

Autologous transplant – the patient's own normal stem cells are collected while in complete remission. Shortly afterwards, high dose chemotherapy or radiation is given. In some cases, the cells are treated to remove any lingering leukaemia cells that may be present, although this is experimental. After the stem cells are collected, they are frozen for use at a later time. After chemotherapy or radiation is complete, the harvested cells are thawed and returned by IV infusion.

Because the transplanted stem cells do not come from another person, there is no 'graft versus host' disease. This helps reduce some of the side effects of treatment, but in general it also makes autologous transplantation somewhat less effective than allogeneic transplantation in fighting the leukaemia, because of the lack of a 'graft versus leukaemia' effect. Autologous transplantation is less often recommended for treatment of AML for this reason.
(Uptodate).

New approaches for the immunotherapy of acute myeloid leukaemia - acute myeloid leukaemia (AML) is a set of related diseases characterised by the immortalisation and uncontrolled expansion of myeloid precursor cells. Core therapy for AML has remained unchanged for nearly 30 years, and survival rates remain unsatisfactory. However, advances in the immunotherapy of AML have created opportunities for improved outcomes.

Enforcing a tumour-specific immune response through the re-direction of the adaptive immune system, which links remarkable specificity with potent cytotoxic effector functions, has proven particularly compelling. This may be coupled with immune checkpoint blockade and conventional therapies for optimal effect.

Engineered antibodies are currently in use in AML and the repertoire of available therapeutics will expand. Natural killer cells (NK cells) have shown effectiveness in this disease. New methods to optimise their activation and the targeting of AML show potential. Most significantly, adoptive immunotherapy with tumour-specific T cells, and particularly T cells re-directed using genetically introduced TCR or chimeric antigen receptors, have demonstrated promise.
(Geiger & Rubnitz, 2015).

Treatment of Relapse
Unfortunately, relapse is common in AML and may affect half or more of all patients who achieve a remission. Although some patients who relapse will respond well to re-treatment, many will not. There are features of the leukaemia cells, and of the results of initial treatment, that help specialists to predict the likely chances of successful re-treatment. If the doctors feel that re-treatment is unlikely to succeed, patients may be advised that palliative care is more appropriate than intensive therapy. Palliative care is designed to alleviate symptoms and control the disease rather than attempting to achieve a cure. If the doctors feel that this type of care may be more appropriate, they will discuss the options in detail before a treatment plan is decided. It is important to emphasise that palliative care is not synonymous with terminal care; treatment of patients in this situation will seek to extend survival as well as controlling symptoms.

Patients who achieve a second remission, and who are eligible, may be considered for a stem cell transplant. It is important to stress that, for many patients with AML, their age and/or general health may mean that a transplant is deemed unacceptably dangerous.
(Leukaemia and Lymphoma Research).

Long Term Effects of Treatment
One common concern of patients is the effect on fertility. Alkylating agents, nitrosureas and cyclophosphamide may all adversely affect the reproductive system. These drugs may affect sperm production in males causing sterility, although most patients in recent clinical studies have regained normal sperm function on completing their chemotherapy.

It is very important that patients are aware that fertility may be restored after very long periods of no sperm production. For this reason it would be unwise for a sexually active male who is apparently sterile as a consequence of chemotherapy to assume that this will always continue to be the case. In females, chemotherapy without radiotherapy is less likely to lead to sterility.

Permanent infertility is most likely in patients who have received a stem cell transplant following high doses of chemotherapy and/or whole body irradiation. An important consideration for both males and females is whether there is a risk of adverse effects on offspring from the treatment received.

A number of large studies in Britain and abroad have confirmed that there is no increased risk of cancer or of an abnormality in children whose parents received treatment for cancer. There are certain long-term consequences seen only in patients who have received stem cell transplants.
(Leukaemia and Lymphoma Research).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may

also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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