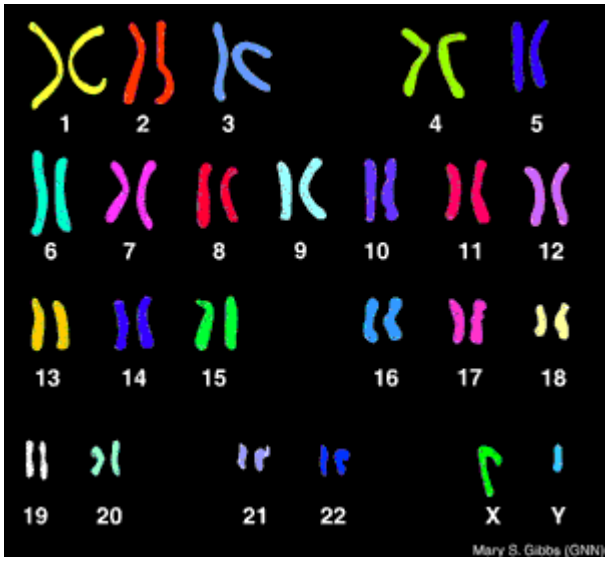
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Adult Acute Promyelocytic Leukaemia (APL)

Introduction

Acute promyelocytic leukaemia (APL) is a form of cancer that affects the stem cells which produce myeloid blood cells in the bone marrow. Myeloid cells are red blood cells, platelets and all white cells except lymphocytes. APL is a sub-type of acute myeloid leukaemia and accounts for about 10% of this form of leukaemia. APL is sometimes referred to as AML M3. There is also a less common form called variant APL, which may be described as M3v. Unlike other forms of acute myeloid leukaemia there are no significant differences in the way APL is treated in children or in adults.



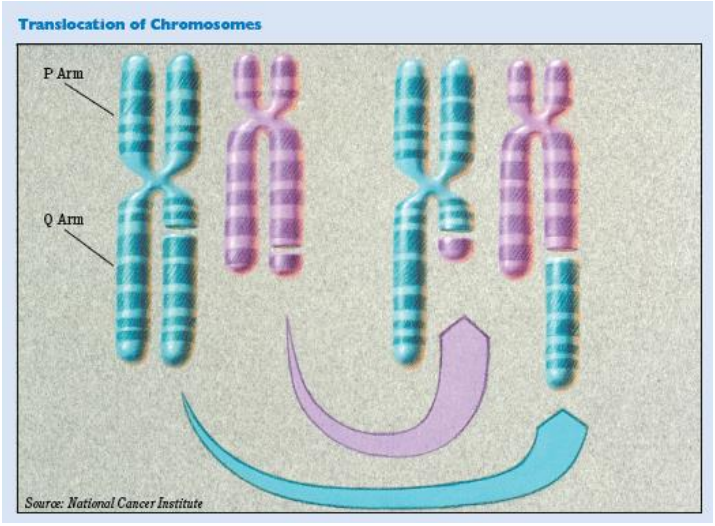
[Picture Credit: Karyotype]

APL is associated with a very specific abnormality in which parts of chromosomes 15 and 17 are swapped over. This is called t(15;17) - the 't' stands for translocation, which means the swapping over of parts of two chromosomes. This joins parts of a gene from each chromosome to produce a fusion gene called PML/RARα which appears to directly cause many of the features of the disease. Treatment with a drug called ATRA (All-Trans Retinoic Acid), which targets the PML/RARα abnormality, has proved very successful. There are other less common fusion genes which can cause APL; which fusion gene is involved influences the way the disease behaves and which treatments may be effective.

In APL the abnormal cells are white blood cells of the neutrophil type. Immature cells known as promyelocytes accumulate in the bone marrow. These are unable to mature (differentiate) properly leading to a significant reduction of normal white blood cells in the circulation. The accumulation of immature cells in the marrow also prevents production of other cell types resulting in anaemia and low platelet counts. Leukaemia cells tend to spill-over into the bloodstream, which is when they can be picked up by a blood test, leading to a diagnosis in most cases.
(Leukaemia & Lymphoma Research; Genetics Home Reference).

Acute Promyelocytic Leukaemia

Acute promyelocytic leukaemia (APML, APL) is a subtype of acute myelogenous leukaemia (AML), a cancer of the white blood cells. In APL, there is an abnormal accumulation of immature granulocytes called promyelocytes. The disease is characterised by a chromosomal translocation involving the retinoic acid receptor alpha (*RARα* or *RARA*) gene and is distinguished from other forms of AML by its responsiveness to all-trans retinoic acid (ATRA; also known as tretinoin) therapy.



[Picture Credit: Chromosomal Translocation]

APL represents a medical emergency with a high rate of early mortality, often due to haemorrhage from a characteristic coagulopathy (abnormal blood coagulation). It is critical to start treatment with a differentiation agent (e.g., all-trans retinoic acid) without delay as soon as the diagnosis is suspected based upon cytologic criteria, and even before definitive cytogenetic or molecular confirmation of the diagnosis has been made.

Acute promyelocytic leukaemia was first described as an entity in the late 1950s in Norway and France as a hyperacute fatal illness associated with a haemorrhagic syndrome. In 1959, Jean Bernard, *et al.* described the association of APL with a severe haemorrhagic diathesis (a congenital, often hereditary, predisposition of the body to a disease) that lead to disseminated intravascular coagulation (DIC) and hyperfibrinolysis. By 1973, there were reports of complete remissions with treatment of the disease by daunorubicin.

In 1974, Leo Sachs pioneered research on leukaemic cell differentiation *in vivo*. Dr. Zhen Yi Wang, a Chinese haematologist, shared data on the efficacy of all-trans retinoic acid (ATRA) in acute promyelocytic leukaemia (APL) patients during a visit to France in 1985. There were several publications in 1990 that linked a translocation between chromosomes 15 and 17 to the pathology of APL. In the early to mid 1990s, arsenic trioxide (ATO) was added to the treatment of APL. A potentially fatal complication of ATRA treatment, called retinoic acid syndrome, was also described. Over the past 50 years, acute APL has transformed from a highly fatal disease to a highly curable disease.
(Medscape; Uptodate).

What Other Names People Use for Acute Promyelocytic Leukaemia

The following are all names used when referring to acute promyleocytic leukaemia:

- AML M3
- APL
- leukaemia, acute promyelocytic
- M3 ANLL
- myeloid leukaemia, acute, M3

(Genetics Home Reference).

Incidence of Adult Acute Promyelocytic Leukaemia in South Africa

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.

Signs and Symptoms of Promyelocytic Leukaemia

There are no specific symptoms of acute promyelocytic leukaemia (APL) and the condition can be confused with other common illnesses. In general APL develops very quickly and the symptoms appear over a matter of days or weeks.

Common symptoms include:

- Unusual bleeding and bruising

- Paleness
- Tiredness and breathlessness
- Frequent and persistent infections

These are caused by a lack of healthy red and white cells and platelets in the blood. Bleeding is a serious symptom of APL and needs immediate medical attention.

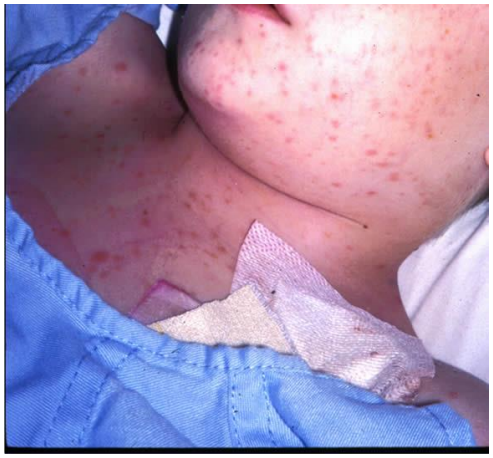
Other less common symptoms include:
- Bone pain due to a build-up of cancer cells in the bone marrow
- Swollen glands due to a build-up of cancer cells in the lymph nodes
- Abdominal pain due to a swollen liver or spleen

Some people with APL may also develop small lumps on their skin, called chloromas, but this is very uncommon. These form when leukaemia cells cluster under the skin. Very few people experience symptoms such as dizziness and bad circulation. This happens when leukaemia cells interfere with the blood supply to the central nervous system.

People with APL may experience all, or just some, of these symptoms.
(Leukaemia and Lymphoma Research).

Can Acute Promyelocytic Leukemia be Inherited?
Acute promyelocytic leukaemia is not inherited but arises from a translocation in the body's cells that occurs after conception.
(Genetics Home Reference).

Clinical Presentation of Acute Promyelocytic Leukaemia
More than 50 percent of all APL patients have pronounced coagulation disorders including a high risk of life-threatening intracerebral haemorrhages as well as bleeding into the skin, the mucous membranes, the gastrointestinal tract, and the lungs referred to as DIC (disseminated intravascular coagulation). The bleeding tendency depends on the severity of thrombocytopenia (relative decrease of platelets in blood).



Disseminated intravascular coagulation, or DIC, is a condition in which blood clots form throughout the body's small blood vessels. These blood clots can reduce or block blood flow through the blood vessels, which can damage the body's organs.

[Picture Credit: Purpuric Rash]

In DIC, the increased clotting uses up platelets and clotting factors in the blood. Platelets are blood cell fragments that stick together to seal small cuts and breaks on blood vessel walls and stop bleeding. Clotting factors are proteins needed for normal blood clotting. With fewer platelets and clotting factors in the blood, serious bleeding can occur. DIC can cause internal and external bleeding.

Internal bleeding occurs inside the body. External bleeding occurs underneath or from the skin or mucosa. The mucosa is the tissue that lines some organs and body cavities, such as the nose and mouth. DIC can cause life-threatening bleeding.

As is the case with all other forms of acute leukaemia the symptoms of pancytopenia may be prominent. Characteristic are fatigue, deterioration of physical fitness, pallor etc. due to anaemia, as well as enhanced susceptibility to infections resulting from neutropenia. Neutropenia refers to an abnormally low number of neutrophils. Neutrophils usually make up 50-70% of circulating white blood cells and serve as the primary defence against infections by destroying bacteria in the blood. Hence, patients with neutropenia are more susceptible to bacterial infections and, without prompt medical attention, the condition may become life-threatening and deadly (neutropenic sepsis). Thromboembolic complications which might also affect large vessels are rare.
(Oncopedia-Guidelines; National Heart, Lung and Blood Institute; Mayo Clinic).

Diagnosis of Promyelocytic Leukaemia
In addition to the standard diagnostic procedures in patients with acute leukaemia, specific APL analyses are required to confirm the diagnosis.

The diagnosis should be immediately confirmed by means of RT-PCR (reverse transcription-polymerase chain reaction is the most sensitive technique for mRNA detection and quantitation currently available), FISH or immunofluorescence. FISH (fluorescence *in situ* hybridization) for the specific translocation and immunofluorescence for expression of PML (progressive multifocal leukoencephalopathy) are considered as equivalent for this purpose. However, the determination of the PML/RARA isoform (bcr1, bcr2, bcr3) by means of RT-PCR will be required for the later monitoring of minimal residual disease (MRD). Monitoring cannot be carried out by applying any other method.

A diagnosis can be confirmed by means of:

- Case history and physical examination (with special attention to bleeding tendency, anaemic symptoms and infections)
- Complete full blood count, including leukocyte count with differential cell counts
- Bone-marrow aspirate including:
    - Cytology
    - Cytochemistry
    - Immunophenotyping
    - FISH (t(15;17)) or immunofluorescence (PML)
    - Cytogenetics (conventional)
- Bone-marrow histology in case of *punctio sicca* (where the aspiration gives no blood cells)
- Coagulation status including Quick's test (a one-step test for the amount of prothrombin present in blood plasma and for determination of prothrombin clotting time), PTT (a performance indicator measuring the efficacy of both the 'intrinsic' and the common coagulation pathways), fibrinogen, D-dimers (D-dimer tests are ordered, along with other laboratory tests and imaging scans, to help rule out the presence of a thrombus or blood clot. Some of the conditions that the d-dimer test is used to help rule out include deep vein thrombosis, pulmonary embolism and strokes)

Additional diagnostic procedures include:

- General health condition by means of the ECOG/WHO Score [The Eastern Cooperative Oncology Group (ECOG) score (published by Oken *et al.* in 1982), also called the WHO or Zubrod score (after C Gordon Zubrod). It runs from 0 to 5, with 0 denoting perfect health and 5 death]
- Evaluation of co-morbidities
- Clinical chemistry, urine analysis
- Hepatitis and HIV serology
- Pregnancy test (if applicable)
- Chest X-ray
- Electrocardiogram (ECG)
- Echocardiography (in case of previous cardiac disease)

(Oncopedia-Guidelines).

Treatment of Promyelocytic Leukaemia

Treatment for patients with acute promyelocytic leukaemia (APL), the M3 subtype of acute myeloid leukaemia (AML), differs from treatment for patients with other AML subtypes. APL is one of the most frequently cured AML subtypes.

APL affects marrow cells called promyelocytes, which form after myeloblast development. The promyelocytes have abnormal chromosome changes, usually an exchange (translocation) of pieces of chromosomes 15 and 17.

Drugs commonly used to treat APL are:

- all-*trans* retinoic acid
- arsenic trioxide

All-*Trans* Retinoic Acid - All-*trans* retinoic acid (ATRA), a substance that comes from vitamin A, often brings APL into remission. ATRA is also known as tretinoin. Retinoic acid helps the promyelocytes affected by APL develop into fully functioning cells (neutrophils). This process reduces the number of leukaemic blast cells in the marrow. And since ATRA also helps improve blood cell counts, it often lessens the side effects of chemotherapy.

At least 80 percent of patients undergo short-term remission when ATRA is used alone. For long-lasting remission, ATRA treatment is combined with chemotherapy during or after induction therapy. For APL patients who have a white cell count of 10,000 per microliter or greater when they're diagnosed, the chemotherapy drug cytarabine is sometimes added during induction or post-remission therapy.

About 70 percent to 80 percent of APL patients go into remission after being treated with ATRA and an anthracycline, such as idarubicin (Idamycin®). Nevertheless, some setbacks can occur, such as:

- haemorrhage (heavy bleeding) during the treatment's initial phases
- resistance to treatment
- the return of APL (relapse)

Patients in remission must get long-term follow-up care to determine whether they are cured or need further therapy. The ideal duration of maintenance therapy is also being

investigated. Currently, it consists of 2 years of 6-mercaptopurine (6-MP), methotrexate, and ATRA.

Arsenic Trioxide - the drug arsenic trioxide (ATO) (Trisenox®) is sometimes given to APL patients if:

- their leukaemia has returned
- their leukaemia cannot be controlled with chemotherapy and ATRA
- they've developed persistent minimal residual disease (MRD - when a low level of remaining APL cells can't be detected by standard tests) - after post-remission therapy

Patients who do not have a donor, or cannot have an allogeneic stem cell transplant for other reasons, may be candidates for an autologous stem cell transplantation. Arsenic trioxide is approved to treat APL patients who have relapsed or are resistant to treatment with chemotherapy and ATRA.
(Leukaemia and Lymphoma Society).

Cancer targeted therapy - acute promyelocytic leukaemia (APL) is a distinct subtype of acute myeloid leukaemia. Morphologically, it is identified as the M3 subtype of acute myeloid leukaemia by the French-American-British classification and cytogenetically is characterised by a balanced reciprocal translocation between chromosomes 15 and 17, which results in the fusion between promyelocytic leukaemia (*PML*) gene and retinoic acid receptor α (*RAR*α).

It seems that the disease is the most malignant form of acute leukaemia with a severe bleeding tendency and a fatal course of only weeks. Chemotherapy (CT; daunorubicin, idarubicin and cytosine arabinoside) was the front-line treatment of APL with a complete remission (CR) rate of 75% to 80% in newly diagnosed patients. Despite all these progresses, the median duration of remission ranged from 11 to 25 months and only 35% to 45% of the patients could be cured by CT.

Since the introduction of all-*trans* retinoic acid (ATRA) in the treatment and optimization of the ATRA-based regimens, the CR rate was raised up to 90% to 95% and 5-year disease free survival (DFS) to 74%. The use of arsenic trioxide (ATO) since early 1990s further improved the clinical outcome of refractory or relapsed as well as newly diagnosed APL. In this article, we review the history of introduction of ATRA and ATO into clinical use and the mechanistic studies in understanding this model of cancer targeted therapy.
(American society of Hematology).

Prognosis (Outlook) of Promyelocytic Leukaemia
The overall prognosis for adults with APL is better than for patients with other forms of acute myeloblastic leukaemia (AML), although it still depends to some extent on individual patient-specific factors (e.g. age, general fitness) and on features of the disease (e.g. whether it is M3v or PML/RARαnegative).

Almost all patients can expect to achieve a good first remission. Patients who are free of disease at the end of consolidation treatment have a good chance of being cured. In younger, fitter patients a cure rate of 70-80% is achievable.

Patients are considered to be at high risk of a haematological relapse if treatment has not achieved a complete remission by the end of consolidation or if the patient experiences a molecular relapse. These patients may be offered a stem cell transplant.
(Leukaemia & Lymphoma Research).

Follow-up

The main purpose of follow-up of patients treated for AP|L is the detection of relapse and of treatment complications. During the first year following completion of chemotherapy, patients are normally checked every one to two months. Checks then gradually become less frequent until they are given annually at five years and beyond. Long-term follow-up is particularly important for those patients who have received treatments that may affect the function of their heart.

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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