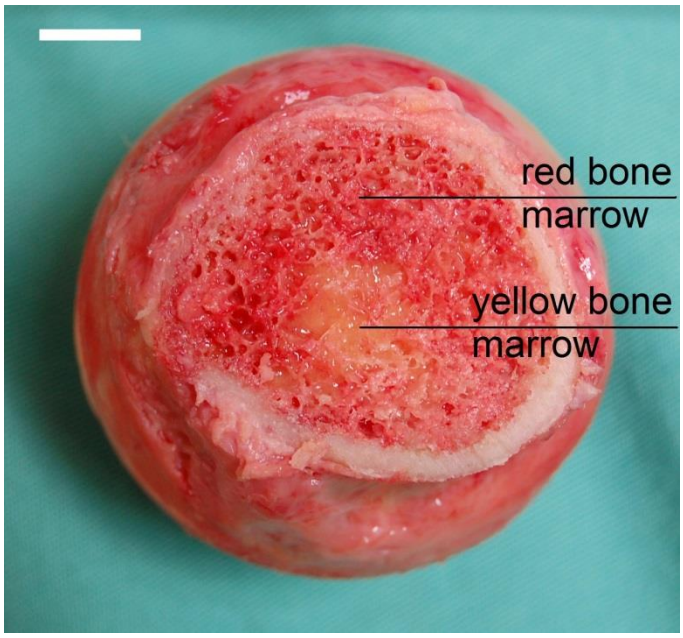
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Multiple Myeloma

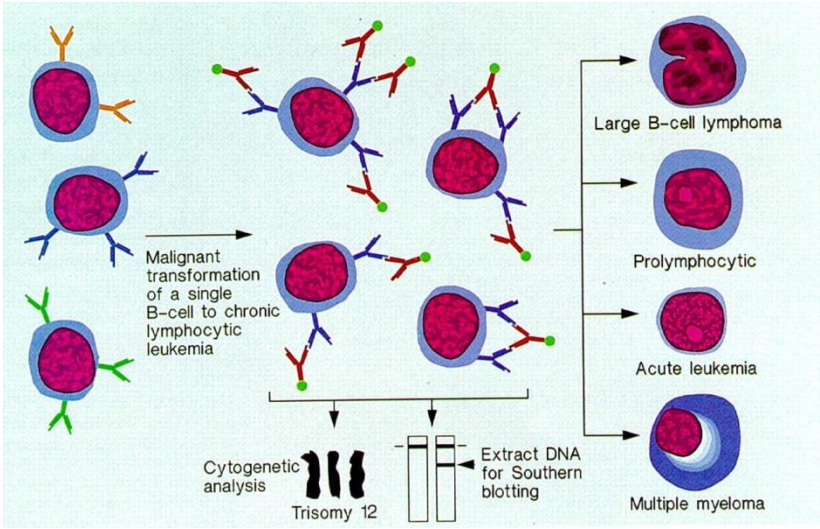
Introduction

Multiple myeloma, also known as myeloma, is a haematologic cancer, or cancer of the blood. It is the second most common blood cancer, after non-Hodgkin's lymphoma and represents approximately 1% of all cancers in white individuals and 2% of all cancers in black individuals.



[Picture Credit: Bone Marrow]

Multiple myeloma develops in the bone marrow, the soft, spongy centre of most bones. Myeloma typically occurs in bone marrow with the most activity, which is the marrow in the spine, pelvic bones, ribs and area of the shoulders and hips. Many blood cells are produced in the bone marrow; myeloma affects plasma cells, cells that produce immunogobulins (antibodies) that help fight infection and disease.



[Picture Credit: Malignant Myeloma Cells]

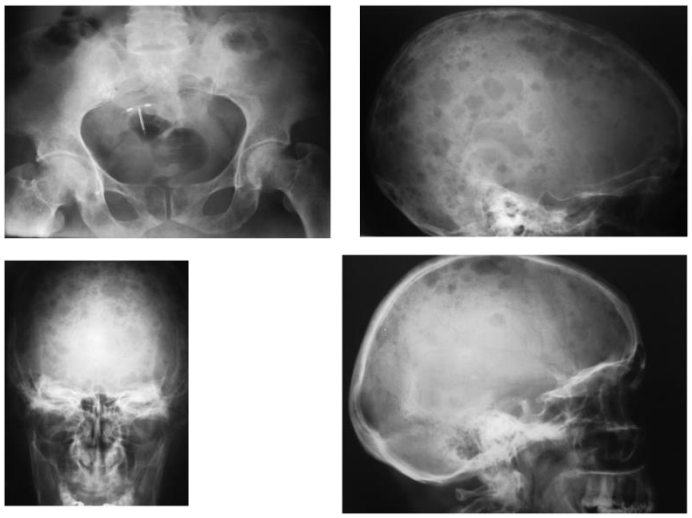
In multiple myeloma, normal plasma cells transform into malignant myeloma cells and produce large quantities of an abnormal immunoglobulin called monoclonal (M) protein. The malignant cells also crowd out and inhibit the production of normal blood cells and antibodies in the bone marrow. In addition, groups of myeloma cells cause other cells in the bone

marrow to remove the solid part of the bone and cause soft spots in the bone. These soft spots, also called osteolytic lesions, and other signs of bone loss are common, although they do not occur in all individuals with myeloma.
(Multiple Myeloma Research Foundation).

Osteolytic Lesions

Osteolytic lesions, also called osteoclastic lesions or lytic lesions (for short), are characteristic areas of damage caused by myeloma. When myeloma invades bone tissue, it causes weak areas to form. In addition, the myeloma cells release chemicals that also lead to bone breakdown. The result is lesions with a specific 'punched-out' appearance that may occur in any bone in the body, but are most often noted in the spine, skull, pelvis and ribs (About.Com).

[Picture Credit: Osteolytic Lesions]



Incidence of Multiple Myeloma in South Africa

According to the National Cancer Registry (2012) the following numbers of Myeloma cases were histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	150	1:1 112	0,41%
Asian males	1	1:112 393	0,12%
Black males	72	1:1 737	0,62%
Coloured males	19	1:638	0,44%
White males	58	1:591	0,29%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	164	1:1 024	0,44%
Asian females	3	1:3 003	0,29%
Black females	93	1:1 266	0,56%
Coloured females	24	1:586	0,58%
White females	43	1:752	0,27%

The frequency of histologically diagnosed cases of Myeloma 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	0	0	11	19	25	36	23	17
Asian males	0	0	0	0	0	0	0	1
Black males	0	0	9	12	24	14	7	3
Coloured males	0	0	1	0	7	5	3	2
White males	0	0	1	5	10	16	12	10

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	0	1	6	13	28	65	39	11
Asian females	0	0	0	0	2	0	1	0
Black females	0	1	6	9	20	31	16	4
Coloured females	0	0	0	1	4	11	5	2
White females	0	0	0	2	1	20	13	5

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.

Symptoms of Multiple Myeloma

Myeloma may not cause any symptoms in the early stages of the disease. Occasionally, it is diagnosed following a routine blood test before any symptoms develop.

When symptoms do happen, they are mostly caused by a build-up of abnormal plasma cells in the bone marrow, and by the presence of the para-protein in the blood.

Bone pain - The most common symptom of myeloma is bone pain. About 70% of people (7 in 10) complain of lower back pain, or pain in their ribs. The pain happens because too many abnormal plasma cells are crowding out the bone marrow, which can damage the bone. Other bones may be affected too, such as the skull or pelvis

Other symptoms include:
These may include:

- tiredness and fatigue due to a lack of red blood cells (anaemia)
- kidney problems, which are caused by the para-proteins produced by the myeloma cells. They can also cause tiredness and anaemia
- repeated infections, particularly chest infections, due to a shortage of normal antibodies
- loss of appetite, feeling sick, constipation, depression and drowsiness, which are caused by too much calcium in the blood (hypercalcaemia)
- unexplained bruising and abnormal bleeding, for example nosebleeds or bleeding gums, due to a reduced number of platelets in the blood
- weight loss

If a person has any of these symptoms, it is important to see a doctor as soon as possible. Many of these symptoms can occur in other conditions - most people with these symptoms will not have multiple myeloma.
(MacMillan Cancer Support).

Causes and Risk Factors for Multiple Myeloma
No cause for myeloma has so far been identified. Some research has suggested possible associations with a decline in the immune system, specific occupations, exposure to certain chemicals, and exposure to radiation.

The likelihood of multiple myeloma is higher than average among people in agricultural occupations, petroleum workers, workers in leather industries and cosmetologists. Exposure to herbicides, insecticides, petroleum products, heavy metals, plastics, and various dusts including asbestos also appear to be risk factors for the disease. However, none of these associations is strong, and in most cases, multiple myeloma develops in individuals who have no known risk factors.

Genetic factors may also be involved in the development of multiple myeloma. Learn more about genetic abnormalities in multiple myeloma. Researchers believe that multiple myeloma is most likely the result of several factors acting together.

The most significant risk factor for multiple myeloma is age, as 96% of cases are diagnosed in people older than 45 years, and more than 63% are diagnosed in people older than 65 years. Thus, it is thought that susceptibility to myeloma may increase with the aging process. It is uncommon for myeloma to develop in more than one member of a family. This means that if you have myeloma, you probably do not need to worry about the disease developing in another family member. There is a slightly increased risk of myeloma occurring in children or siblings of individuals who have the disease.
(Multiple Myeloma Research Foundtion).

Diagnosis of Multiple Myeloma
The following tests can be done to diagnose multiple myeloma

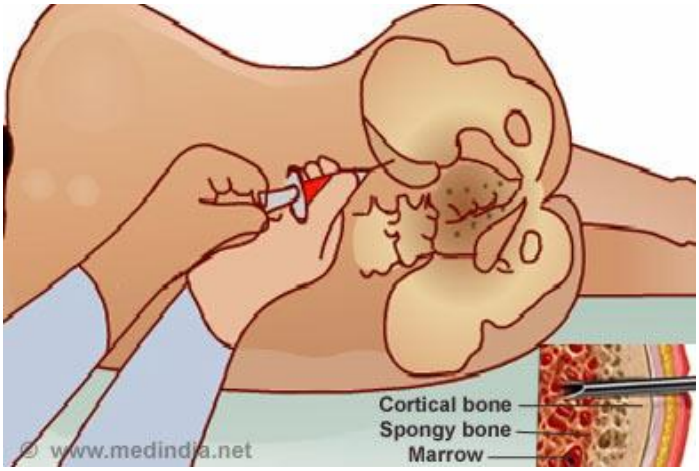
A blood test called serum protein electrophoresis separates the blood proteins and can detect the presence of monoclonal proteins (M proteins) — referred to as an "M spike" — in the blood.

Parts of M proteins may also be detected in a test of one's urine. When M proteins are found in urine, it is referred to as Bence Jones proteins. Monoclonal proteins may indicate multiple myeloma, but also can indicate other conditions.

If the doctor discovers M proteins, additional blood tests may be required to measure blood cell counts and levels of calcium, uric acid and creatinine. The doctor may also conduct other blood tests to check for beta-2-microglobulin — another protein produced by myeloma cells — or to measure the percent of plasma cells in the bone marrow.

Other tests may include:
Imaging - X-rays of the skeleton can show whether the bones have any thinned-out areas (osteolytic lesions), common in multiple myeloma. If a closer view of the bones is necessary, the doctor may use magnetic resonance imaging (MRI), computerised tomography (CT) scanning or positron emission tomography (PET) scanning.

Bone marrow examination - the doctor may also conduct a bone marrow examination (biopsy) by using a needle to remove a small sample of bone marrow tissue. The sample is then examined under a microscope to check for myeloma cells. A portion of the sample is also tested for chromosome abnormalities using tests such as fluorescence *in situ* hybridisation (FISH).



[Picture Credit: Bone Marrow Biopsy]

Tests are also done to measure the rate at which the plasma cells are dividing. (Mayo Clinic).

Staging of Multiple Myeloma

Staging is the process of finding out how much the cancer has advanced. It is important for treatment options and prognosis. *Prognosis* is a prediction of the course of disease — the outlook for survival. Knowing all one can about staging lets one take a more active role in making informed decisions about one's treatment.

Multiple myeloma may be staged using the Durie-Salmon system. Although some doctors use this system, its value is becoming limited because of newer diagnostic methods. Recently, a new staging system called the *International Staging System for Multiple Myeloma* has been developed. It relies mainly on levels of albumin and beta-2-microglobulin in the blood. Other factors that may be important are kidney function, platelet count and the patient's age.

The Durie-Salmon Staging System for Multiple Myeloma

This system is based on 4 factors:

- the amount of abnormal monoclonal immunoglobulin in the blood or urine: Large amounts of monoclonal immunoglobulin indicate that many malignant plasma cells are present and are producing that abnormal protein
- the amount of calcium in the blood: High blood calcium levels can be related to advanced bone damage. Because bone normally contains lots of calcium, bone destruction releases calcium into the blood
- the severity of bone damage based on x-rays: Multiple areas of bone damage seen on x-rays indicate an advanced stage of multiple myeloma
- the amount of hemoglobin in the blood: Hemoglobin carries oxygen in red blood cells. Low hemoglobin levels mean you are anemic and can indicate that the myeloma cells occupy much of the bone marrow and that not enough space is left for the normal marrow cells to make enough red blood cells

This system uses these factors to divide myeloma into 3 stages. Stage I indicates the smallest amount of tumor, and stage III indicates the largest amount of tumor:

Stage I - a relatively small number of myeloma cells are found. All of the following features must be present:

- haemoglobin level is only slightly below normal (still above 10 g/dL)
- bone X-rays appear normal or show only 1 area of bone damage
- calcium levels in the blood are normal (less than 12 mg/dL)
- only a relatively small amount of monoclonal immunoglobulin is in blood or urine

Stage II - a moderate number of myeloma cells are present. Features are between stage I and stage III

Stage III - a large number of myeloma cells are found. One or more of the following features must be present:

- low haemoglobin level (below 8.5 g/dL)
- high blood calcium level (above 12 mg/dL)
- 3 or more areas of bone destroyed by the cancer
- large amount of monoclonal immunoglobulin in blood or urine

The International Staging System

This system divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels.

Stage I - serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/L)

Stage II - neither stage I or III, meaning that either:

- the beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level),

OR

- the albumin is below 3.5 while the beta-2 microglobulin is less than 3.5

Stage III - serum beta-2 microglobulin is greater than 5.5.
(American Cancer Society).

Treatment of Multiple Myeloma

Because currently there is no known cure for multiple myeloma, understanding the standard treatments - and the treatment options - is critical in attempting to prolong survival and maintain the patient's overall functional ability and quality of life. Aspects of importance in the treatment of multiple myeloma include:

- Which patients with multiple myeloma are candidates for an approach known as ‘watchful waiting’, where the progress of the disease is monitored carefully but no specific treatment is required
- The various phases in the treatment of multiple myeloma for patients whose disease has progressed to the point where treatment becomes necessary. These treatment phases are grouped into the following categories:
  - initial or induction chemotherapy
  - consolidation therapy
  - maintenance therapy
  - salvage therapy

- The role of stem cell transplantation in the management of patients with multiple myeloma, including the risks and benefits of this procedure

- The treatment options available to patients with multiple myeloma who experience a relapse or recurrence of the disease after initially having gone into remission
- The role of plasmapheresis - the direct removal of abnormal antibody proteins from the bloodstream - in the management of patients with multiple myeloma
- A detailed overview of the risk of infections in people with multiple myeloma, including practical recommendations for reducing the risks of developing potentially life-threatening bacterial, viral, and fungal infections
- The treatment options that are available for the management of patients with multiple myeloma who develop myeloma bone disease - areas of bone destruction caused by multiple myeloma that significantly increase the risk of developing pathologic fractures
- The prognosis (outlook) for people with multiple myeloma and important prognostic factors that have a significant impact in predicting the overall chances of recovery and survival
- The role of complementary therapies in the management of people with multiple myeloma
- Quality of life issues such as sleep disorders, fatigue, weight loss, and psychological stress that often confront people with multiple myeloma and tips for how to minimize their impact and better cope with these important issues

(Medifocus).

If one has multiple myeloma and is not experiencing any symptoms, he/she may not need treatment. However, the doctor will regularly monitor the patient's condition for signs the disease is progressing. If it is, the patient may need treatment.

If one is experiencing symptoms, treatment can help relieve pain, control complications of the disease, stabilise the condition and slow the progress of the disease.

Standard treatments for multiple myeloma

Though there's no cure for multiple myeloma, with good treatment results one can usually return to near-normal activity.

Standard treatment options include:

Bortezomib (Velcade). Bortezomib was the first approved drug in a new class of medications called proteasome inhibitors. It is administered intravenously. It causes cancer cells to die by blocking the action of proteasomes. It is approved for people with newly diagnosed and previously treated myeloma.

Thalidomide (Thalomid). Thalidomide, a drug originally used as a sedative and to treat morning sickness during pregnancy in the 1950s, was removed from the market after it was found to cause severe birth defects. However, the drug received approval from the Food and Drug Administration (FDA) again in 1998, first as a treatment for skin lesions caused by leprosy. Today thalidomide is FDA approved for the treatment of newly diagnosed multiple myeloma. This drug is given orally.

Lenalidomide (Revlimid). Lenalidomide is chemically similar to thalidomide, but because it appears to be more potent and cause fewer side effects, it is currently used more often than thalidomide. Lenalidomide is given orally. It is approved for people with previously treated myeloma, but is also often used in people with newly diagnosed disease.

Chemotherapy. Chemotherapy involves using medicines — taken orally as a pill or given through an intravenous (IV) injection — to kill myeloma cells. Chemotherapy is often given in cycles over a period of months, followed by a rest period. Often chemotherapy is

discontinued during what is called a plateau phase or remission, during which your M protein level remains stable. You may need chemotherapy again if your M protein level begins to rise. Common chemotherapy drugs used to treat myeloma are melphalan (Alkeran), cyclophosphamide (Cytoxan), vincristine, doxorubicin (Adriamycin) and liposomal doxorubicin (Doxil).

Corticosteroids. Corticosteroids, such as prednisone and dexamethasone, have been used for decades to treat multiple myeloma. They are typically given in pill form.

Stem cell transplantation. This treatment involves using high-dose chemotherapy — usually high doses of melphalan — along with transfusion of previously collected immature blood cells (stem cells) to replace diseased or damaged marrow. The stem cells can come from you or from a donor, and they may be from either blood or bone marrow.

Radiation therapy. This treatment uses high-energy penetrating waves to damage myeloma cells and stop their growth. Radiation therapy may be used to quickly shrink myeloma cells in a specific area — for instance, when a collection of abnormal plasma cells form a tumor (plasmacytoma) that's causing pain or destroying a bone.

Initial therapy for multiple myeloma

The initial chemotherapy used to treat multiple myeloma depends on whether the patient is considered a candidate for stem cell transplantation and his/her individual risk profile. Factors such as the risk of the disease progressing, the age and general health play a part in determining whether stem cell transplantation may be right.

If considered a candidate for stem cell transplantation, the initial therapy will likely exclude melphalan because this drug can have a toxic effect on stem cells, making it impossible to collect enough of them. The first treatment will typically be lenalidomide or bortezomib combined with low-dose dexamethasone.

The stem cells will likely be collected after the patient has undergone three to four months of treatment with these initial agents. The patient may undergo the stem cell transplant soon after the cells are collected or the transplant may be delayed until after a relapse, if it occurs. The age and personal preference of the patient are important factors in determining when to do the transplant.

After the stem cell transplantation, the patient will likely start a new course of treatment with a drug combination that includes bortezomib and melphalan.

If not considered a candidate for stem cell transplantation, the initial therapy is likely to be a combination of melphalan, prednisone and thalidomide — often called MPT — or melphalan, prednisone and bortezomib (Velcade) — often called MPV. If the side effects are intolerable, melphalan plus prednisone (MP) or lenalidomide plus low-dose dexamethasone are additional options. This type of therapy is typically given for about 12 to 18 months.

Treatments for relapsed or treatment-resistant multiple myeloma

Most people who are treated for multiple myeloma eventually experience a relapse of the disease. In some cases, none of the currently available, first line therapies slow the cancer cells from multiplying. If the patient experiencea a relapse of multiple myeloma, the doctor may recommend repeating another course of the treatment that initially helped. Another

option is trying one or more of the other treatments typically used as first line therapy, either alone or in combination.

Research on a number of new treatment options is ongoing, and these drugs offer important options for those with multiple myeloma. Talk to a doctor about what clinical trials may be available to you.
(Mayo Clinic).

FDA Approves New Combo Regimen for Refractory Multiple Myeloma

On 19 June 2017, Janssen Biotech announced that the Food and Drug Administration (FDA) has approved Darzalex (daratumumab) in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received ≥2 prior therapies including lenalidomide and a proteasome inhibitor (PI).

The FDA approval was based on data from the Phase 1b EQUULEUS study (n=103) that demonstrated an overall response rate (ORR) of 59.2% (95% CI: 49.1, 68.8) with very good partial response (VGPR) seen in 28.2% of patients who were treated with Darzalex 16mg/kg in combination with pomalidomide and low-dose dexamethasone.

Complete response (CR) was seen in 5.8% of patients, stringent CR in 7.8% of patients, and partial response in 17.5% of patients. The median time to response was one month with a median duration of response of 13.6 months.

The safety data of the Darzalex combination therapy was similar to the established profile of Darzalex monotherapy and pomalidomide + dexamethasone, respectively. In the study, the most common adverse reactions were infusion reactions, diarrhoea, constipation, nausea, vomiting, fatigue, pyrexia, upper respiratory tract infection, and others.

Darzalex, a CD38-directed antibody, was initially approved as a monotherapy for patients with multiple myeloma who had received ≥3 prior lines of therapy, including a PI and an immunomodulatory agent. It was later approved for use with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who received ≥1 prior therapy.

Darzalex is supplied as 100mg/5mL and 400mg/20mL strength solutions for intravenous (IV) infusion after dilution.
(MPR).

Treating Complications of Multiple Myeloma

Because multiple myeloma can cause a number of complications, you may also need treatment for those specific conditions.

For example:

- Back pain - taking pain medication or wearing a back brace can help relieve the back pain the patient might experience with multiple myeloma
- Kidney complications - people with severe kidney damage may need dialysis
- Infections - antibiotics may be necessary to help treat infections or to help reduce the risk of them

- Bone loss – the patient may be given medications called bisphosphonates, such as pamidronate (Aredia) or zoledronic acid (Zometa), which bind to the surface of the bones and help prevent bone loss. Treatment with these drugs is associated with the risk of harm to the jawbone. If the patient is taking these medications, avoid dental procedures without consulting a doctor first

- Anaemia - if a patient has persistent anaemia, the doctor may prescribe erythropoietin injections. Erythropoietin is a naturally occurring hormone made in the kidneys that stimulates the production of red blood cells. Research suggests that the use of erythropoietin may increase the risk of blood clots in some people with myeloma

(Mayo Clinic).

Treating Multiple Myeloma with a Measles Virus

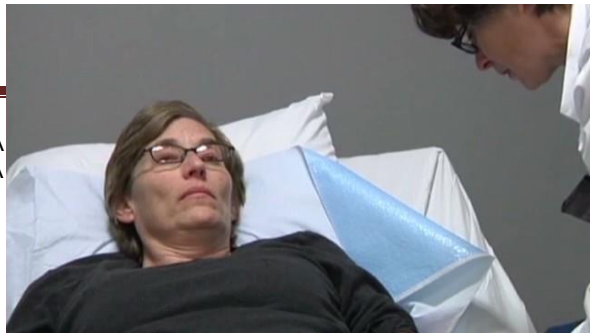
During May 2014 the world was awash with the dramatic news that researchers in the Mayo Clinic, United States of America, had apparently cured a patient with multiple myeloma using a measles virus.

Since the turn of the nineteenth century the existence of viruses that could possibly destroy tumours was first recognised. Early case reports of making use of oncolytic viruses (a virus that preferentially infects and kills cancer cells) form that time reported the shrinking of some cancer tumours during naturally acquired virus infections. This provided the basis for clinical trials where body fluids containing human or animal viruses were used to transmit infections to cancer patients. In most cases the immune of the host destroyed the viruses before they could have any effect. In patients whose immune system was compromised, the viral infection persisted and some of the tumours regressed. With the advent of rodent experimentation and new methods for virus propagation, there were numerous attempts through the 1950s and 1960s to force the evolution of viruses with greater tumour specificity. Success was limited and many researchers abandoned the field. Technology employing reverse genetic modification later brought about a renewal of interest in making use of viruses that allowed the creation of more potent, tumour-specific types of viruses that infects and breaks down cancer cells but not normal cells (Kelly & Russell, 2007).

It is important to know that the virus that used in the Mayo Clinic to treat a case of multiple myeloma, was not a standard measles virus but a measles virus that was specifically engineered (modified) for the purpose of breaking down the myeloma (cancer cells) in two specific patients. Engineered measles viruses were used in this instance because neither of the two patients had previously been immunised against measles and neither of them had any resistance to measles because they did not have measles during their lifetime. This means that they were both measles-seronegative.

Both patients were diagnosed with multiple myeloma. They had both been unsuccessfully treated by means of conventional therapy for between 7 and 9 years respectively and had both received stem cell transplants. Both patients also had multiple recurrences of their disease. They were both given a large single dose (approximately 100 billion units – enough to vaccinate 10 million people had it been a regular vaccine virus) of the specifically engineered virus (MV-NIS virus). Both patients became very ill and regrettably one patient died. The second patient (Ms Stacy Erholtz) received intensive care and support and survived the treatment and was eventually declared to be in remission.

[Picture Credit: Ms Stacy Erholtz]



The best approach to this spectacular news is cautious optimism. There is still much research to be done. Remarkably little is still known about the best way to deliver oncolytic viruses intravenously. The speed and duration of infusion, the quantity of virus, and the number of doses to be administered are also still poorly understood at this time. However, oncolytic viruses offer a promising new modality for the targeted infection and destruction of disseminated cancer (Bell, 2014; Russell, *et al*., 2014).

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.

<u>Use of Placebos</u>

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.

<u>Possible benefits of taking part in a clinical trial</u>

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).

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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