

A Review on Cancer and drug on "Actinomycin D: An Overview of Its Mechanisms of Action

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ABSTRACT

Cancer in the broader sense refers to more than 277 different types of cancer disease. Scientists have identified different stage of cancers, indicating that several gene mutations are involved in cancer pathogenesis. These gene mutations lead to abnormal cell proliferation. Genetic disorders caused by heritance or inheritance factors have a pivotal role in the increase of cell growth. With the assistance of technological advances in bioinformatics and molecular techniques, additional information has been obtained that can be useful for early diagnosis and proper treatment. The effects of drugs on patients with cancer can predict and even manage some aspects of side effects. In recent years, carcinogenesis mechanisms have been detected by molecular genetic studies. The results of these studies led to an improved understanding of the role of genetic disorders in cancer formation. In this study, our aim was to review molecular aspects of cancer.

KEYWORDS

Cancer

Types

Chemotherapy

Pharmacological Treatment

INTRODUCTION

Cancer is the second leading cause of mortality worldwide. Overall, the prevalence of cancer has actually increased; just in the United States alone, approximately 1665540 people suffered from cancer, and 585,720 of them died due to this disease by 2014. Therefore, cancer is a serious problem affecting the health of all human societies. Unfortunately, it is a variety disease at the tissue level and this variety is a major challenge for its specific diagnosis, followed by efficacy of treatment. In men, the highest percentages of cancer types occur in the prostate, lung and bronchus, colon and rectum, and urinary bladder, respectively. In women, cancer prevalence is highest in the breast, lung and bronchus, colon and rectum, uterine corpus and thyroid, respectively. This data indicates that prostate and breast cancer constitute a major portion of cancer in men and women . For children, the highest percentage types of cancer disease are blood cancer,

and cancers related to the brain and lymph nodes, respectively. Cancer occurs by a series of successive mutations in genes so that these mutations change cell functions. Chemical compounds have an obvious role of forming gene mutations and cancer cells.



In addition, smoking involves several carcinogenic chemical compounds that lead to lung cancer. Interestingly, environmental chemical substances with carcinogenic properties influence directly or indirectly the cytoplasm and nucleus of cells, and lead to genetic disorders and gene mutations. Viruses, bacteria and radiation rays are other carcinogenesis factors, comprising about 7% of all cancers. In general, cancer disrupts cellular relations and results in the dysfunction of vital genes. This disturbance is affective in the cell cycle, and leads to abnormal proliferation. In addition, the lack of tumor suppressor genes triggers uncontrolled cells division. Normally, repair genes translate to protein and enzymes that have repairing properties and more than 30 types of detected repair proteins.

Classification

Based On Histological Type

- Carcinoma
- Sarcoma
- Myeloma
- Leukemia
- Lymphoma

CARCINOMA

Carcinoma is cancer that forms in epithelial tissue. Epithelial tissues lines most of your organs, the internal passageways in your body (like your esophagus), and your skin. Most cancers affecting your skin, breasts, kidney, liver, lungs, pancreas, prostate gland, head and neck are carcinomas.

Most people think of cancer in terms of where it forms (breast cancer, colon cancer, etc.), but this is just one way to distinguish one type of cancer from another

. Scientists also classify cancers based on the types of tissue where cancer cells start growing.

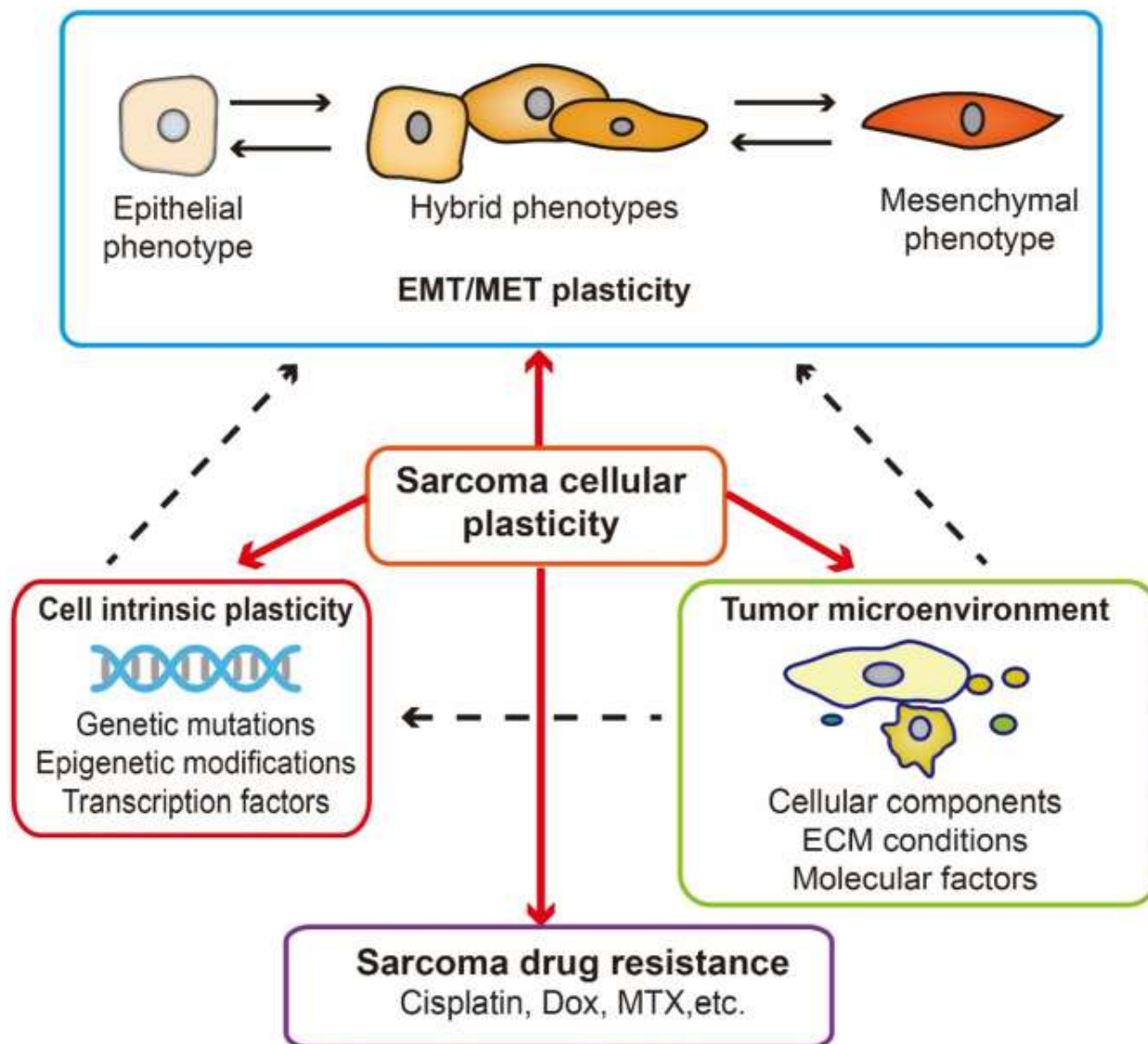


SARCOMA

Sarcoma is a type of cancer that can occur in various locations in your body.

Sarcoma is the general term for a broad group of cancers that begin in the bones and in the soft (also called connective) tissues (soft tissue sarcoma). Soft tissue sarcoma forms in the tissues that connect, support and surround other body structures. This includes muscle, fat, blood vessels, nerves, tendons and the lining of your joints.

There are more than 70 types of sarcoma. Treatment for sarcoma varies depending on sarcoma type, location and other factors.



MYELOMA

Myeloma is a type of blood cancer that develops from cells in the bone marrow called plasma cells. Bone marrow is the spongy tissue found inside the inner part of some of our large bones. The bone marrow produces different types of blood cells.

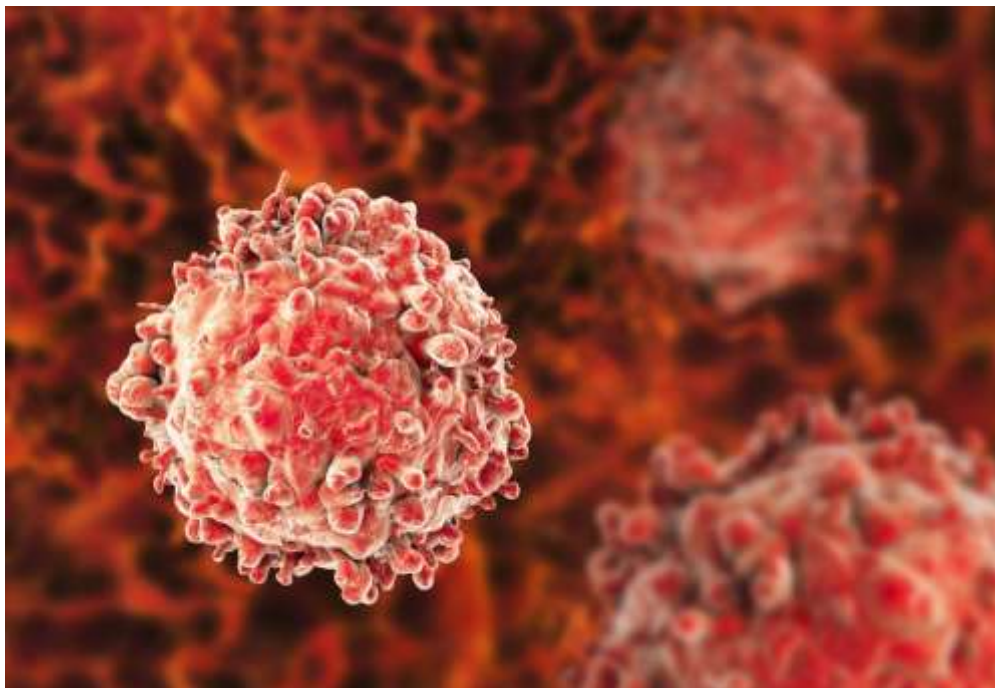


LEUKEMIA

Leukemia is cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system.

Many types of leukemia exist. Some forms of leukemia are more common in children. Other forms of leukemia occur mostly in adults.

Leukemia usually involves the white blood cells. Your white blood cells are potent infection fighters-they normally grow and divide in an orderly way, as your body needs them. But in people with leukemia, the bone marrow produces an excessive amount of abnormal white blood cells, which don't function properly.



LYMPHOMA

Lymphoma is a cancer of the lymphatic system, which is part of the body's germ-fighting network.

The lymphatic system includes the lymph nodes (lymph glands), spleen, thymus gland and bone marrow. Lymphoma can affect all those areas as well as other organs throughout the body.

Many types of lymphoma exist. The main subtypes are:

-Hodgkin's lymphoma (formerly called Hodgkin's disease)

-Non Hodgkin's lymphoma.



SYMPTOMS AND CAUSES OF CANCER

SYMPTOMS

- Breast changes
- Lump or firm feeling in your breast or under your arm
- Nipple changes or discharge
- Skin that is itchy, red, scaly, dimpled, or puckered

Bladder changes

- Trouble urinating
- Pain when urinating
- Blood in the urine

Bleeding or bruising, for no known reason

Bowel changes

- Blood in the stools
- Changes in bowel habits

Cough or hoarseness that does not go away

Eating problems

- Pain after eating (heartburn or indigestion that doesn't go away)
- Trouble swallowing
- Belly pain
- Nausea and vomiting
- Appetite changes

Fatigue that is severe and lasts

Fever or night sweats for no known reason

Mouth changes

- A white or red patch on the tongue or in your mouth
- Bleeding, pain, or numbness in the lip or mouth

Neurological problems

- Headaches
- Seizures
- Vision changes
- Hearing changes
- Drooping of the face

Skin changes

- A flesh-colored lump that bleeds or turns scaly
- A new mole or a change in an existing mole
- A sore that does not heal
- Jaundice (yellowing of the skin and whites of the eyes)

Swelling or lumps anywhere such as in the neck, underarm, stomach, and groin

Weight gain or weight loss for no known reason

ETIOLOGY/CAUSES

- Cigarette Smoking
- Exposure to Sun and Tanning Beds.
- Overweight and Obesity.
- Excessive Alcohol Use.
- Infectious Disease.
 - Age.
 - Alcohol.
 - Cancer-Causing Substances.
 - Chronic Inflammation.
 - Diet.
 - Hormones.

DIAGNOSTIC TESTS FOR CANCER

Diagnosis:

Cancer screening

Diagnosing cancer at its earliest stages often provides the best chance for a cure. With this in mind, talk with your doctor about what types of cancer screening may be appropriate for you.

For a few cancers, studies show that screening tests can save lives by diagnosing cancer early. For other cancers, screening tests are recommended only for people with increased risk.

A variety of medical organizations and patient-advocacy groups have recommendations and guidelines for cancer screening. Review the various guidelines with your doctor and together you can determine what's best for you based on your own risk factors for cancer.

Cancer diagnosis

Your doctor may use one or more approaches to diagnose cancer:

- **Physical exam.** Your doctor may feel areas of your body for lumps that may indicate cancer. During a physical exam, your doctor may look for abnormalities, such as changes in skin color or enlargement of an organ, that may indicate the presence of cancer.
- **Laboratory tests.** Laboratory tests, such as urine and blood tests, may help your doctor identify abnormalities that can be caused by cancer. For instance, in people with leukemia, a common blood test called complete blood count may reveal an unusual number or type of white blood cells.
- **Imaging tests.** Imaging tests allow your doctor to examine your bones and internal organs in a noninvasive way. Imaging tests used in diagnosing cancer may include a computerized tomography (CT) scan, bone scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, ultrasound and X-ray, among others.
- **Biopsy.** During a biopsy, your doctor collects a sample of cells for testing in the laboratory. There are several ways of collecting a sample. Which biopsy procedure is right for you depends on your type of cancer and its location. In most situations, a biopsy is the only way to definitively diagnose cancer.

In the laboratory, doctors look at cell samples under the microscope. Normal cells look uniform, with similar sizes and orderly organization. Cancer cells look less orderly, with varying sizes and without apparent organization.

TREATMENT

Many cancer treatments are available. Your treatment options will depend on several factors, such as the type and stage of your cancer, your general health, and your preferences. Together you and your doctor can weigh the benefits and risks of each cancer treatment to determine which is best for you.

- **Transplant.** Bone marrow transplant is also known as a stem cell transplant. Your bone marrow is the material inside your bones that makes blood cells. A bone marrow transplant can use your own cells or cells from a donor.

A bone marrow transplant allows your doctor to use higher doses of chemotherapy to treat your cancer. It may also be used to replace diseased bone marrow.

- **Immunotherapy.** Immunotherapy, also known as biological therapy, uses your body's immune system to fight cancer. Cancer can survive unchecked in your body because your immune system doesn't recognize it as an intruder. Immunotherapy can help your immune system "see" the cancer and attack it.

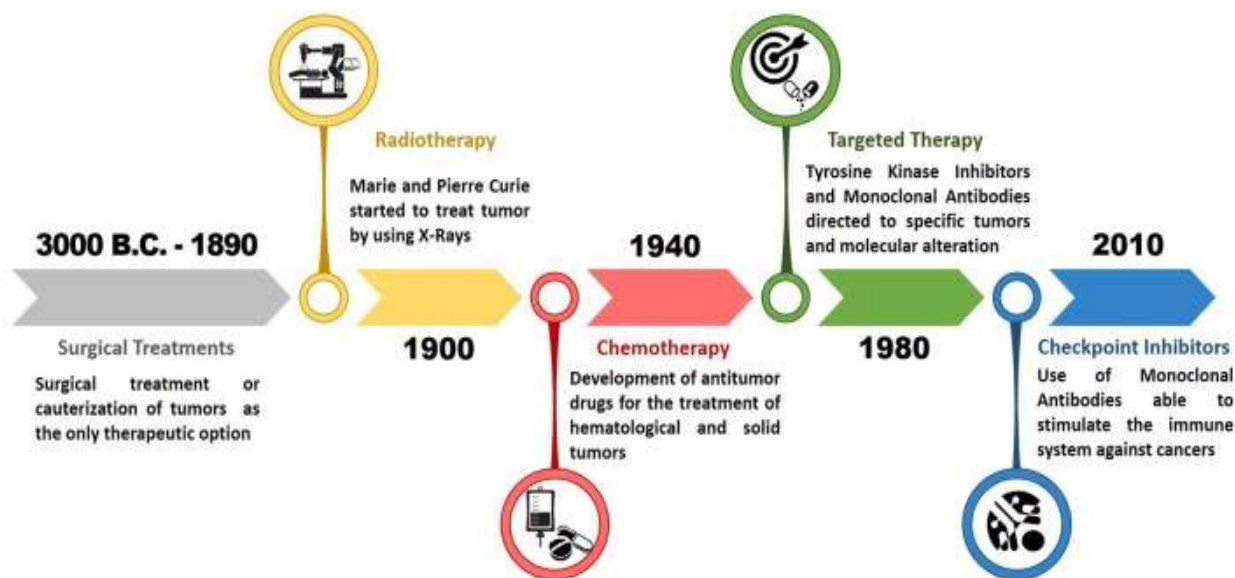
- **Hormone therapy.** Some types of cancer are fueled by your body's hormones. Examples include breast cancer and prostate cancer. Removing those hormones from the body or blocking their effects may cause the cancer cells to stop growing.

Targeted drug treatment focuses on specific abnormalities within cancer cells that allow them to

Cancer treatments

- **Surgery.** The goal of surgery is to remove the cancer or as much of the cancer as possible.
- **Chemotherapy.** Chemotherapy uses drugs to kill cancer cells.
- **Radiation therapy.** Radiation therapy uses high-powered energy beams, such as X-rays and protons, to kill cancer cells. Radiation treatment can come from a machine outside your body (external beam radiation), or it can be placed inside your body.
- **Clinical trials.** Clinical trials are studies to investigate new ways of treating cancer. Thousands of cancer clinical trials are underway.

Other treatments may be available to you, depending on your type of cancer.



DRUGS USED IN CANCER TREATMENT

- Alkylating agents
- Actinomycin-D
- Nitrosoureas
- Antimetabolites
- Anti-tumor antibiotics
- Plant alkaloids
- Corticosteroids
- Miscellaneous drugs that do not fall into any of these categories

Some examples of alkylating agents include:

- Altrephine
- Bendamustine
- Busulfan
- Carboplatin
- Chlorambucil
- Cisplatin
- Cyclophosphamide
- Dacarbazine
- Ifosfamide
- Mechlorethamine
- Melphalan
- Oxaliplatin
- Temozolomide
- Thiotepe
- Trabect
- Edin

ACTINOMYCIN-D

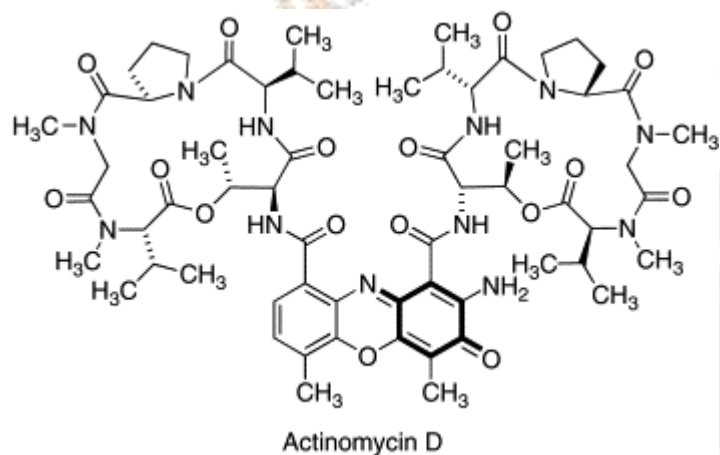
Actinomycin D is a well-known antibiotic of the actinomycin group that exhibits high antibacterial and antitumor activity. Actinomycin D has been widely used in clinical practice since 1954 as an anticancer drug for treating many tumors and it is also a useful tool in biochemistry and molecular biology. According to the Internet bibliographic database -- MEDLINE, actinomycins, and mainly actinomycin D, have been the subject of about 3300 science papers so far, and this paper is a review of the information concerning the mechanisms of action of actinomycin D. There are several mechanisms of its action that are responsible for its cytotoxic and antitumor action, these being associated with DNA functionality, leading to RNA and, consequently, protein synthesis inhibition. The two main mechanisms are intercalation to DNA and the stabilization of cleavable complexes of topoisomerases I and II with DNA, in which a phenoxazone ring localizes between GpC base pair sequence in DNA and polypeptide lactones rings occupy a position in the minor groove of the DNA helix or the drug penetrates to a place in the DNA structure where topoisomerase binds with DNA, respectively. Moreover, the slow dissociation of actinomycin D from DNA complexes, its photodynamic activity and free radical formation, as well as other biochemical effects of activity of actinomycin D may be, as suggested, important factors that influence the biological activity of this drug. In the literature not enough convincing evidence has been proposed that could indicate one particular mechanism of action as responsible for the biological activity of actinomycin D.

Uses of Actinomycin-D

Dactinomycin, also known as Actinomycin D, is a chemotherapy medication used to treat a number of types of cancer. This includes Wilms tumor, rhabdomyosarcoma, Ewing's sarcoma, trophoblastic neoplasm, testicular cancer, and certain types of ovarian cancer. It is given by injection into a vein

A drug that comes from the bacterium *Streptomyces parvulus* and is used alone or with other drugs to treat adults and children with Ewing sarcoma, gestational trophoblastic tumor, rhabdomyosarcoma, Wilms tumor, or certain types of testicular cancer and adults with certain types of solid tumors.

STRUCTURE OF ACTINOMYCIN-D



MECHANISAM AND ACTION OF ACTINOMYCIN-D

- Actinomycin-D intercalates with DNA strands.
- Actinomycin inhibits both DNA synthesis and RNA synthesis by blocking chain elongation.
- They interact with G-C base pairs as they require the two –amino group of guanine for binding.
- Actinomycins are used as anti-cancer drugs.
- Antibiotic, inhibits transcription in bacteria and eukaryotes.
- The Planar portion of the this molecule inserts (intercalates) into the double helical DNA between successive GC base pairs, deforming the DNA.
- Inhibits RNA elongation by restricting RNA polymerase along the template.
- Concentration dependent action.

INDICATIONS AND DOSAGE

Childhood rhabdomyosarcoma, Ewing's sarcoma, Wilm's tumour

Adult: 15 mcg/kg daily for 5 days, in combination regimens. Max: 15 mcg/kg or 400-600 mcg/m² daily for 5 days per 2-wk cycle.

Child: ≥6 mth Same as adult dose.

Intravenous

Metastatic nonseminomatous testicular cancer

Adult: 1 mg/m² on day 1 of combination regimens. Max: 15 mcg/kg or 400-600 mcg/m² daily for 5 days per 2-wk cycle.

Intravenous

Gestational trophoblastic tumours

Adult: 12 mcg/kg daily for 5 days as a single agent or 500 mcg daily on days 1 and 2 of combination regimens. Max: 15 mcg/kg or 400-600 mcg/m² daily for 5 days per 2-wk cycle.

Reconstitution

Add 1.1 mL of sterile water for inj (w/o preservative), using aseptic precautions to make a soln containing approx 500 mcg/mL. The reconstituted soln can be added to infusion soln of dextrose 5% inj or NaCl inj either directly or to the tubing of a running IV infusion.

Incompatibility

Filgrastim.

Contraindications

Hypersensitivity. Patient w/ varicella or herpes zoster infection.

Special Precautions

Patient w/ impaired bone marrow. Renal and hepatic impairment. Pregnancy and lactation.

Adverse Reactions

Nausea, vomiting, cheilitis, oesophagitis, GI ulceration, proctitis, fever, malaise, hypocalcaemia, myalgia, alopecia, pneumonitis, kidney and liver abnormalities, eruptions, acne, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, severe tissue damage, oedema, neutropenia and febrile neutropenia.

Potentially Fatal: Hepatic failure, hepatic veno-occlusive disease, particularly in childn <4 yr, myelosuppression, sepsis, including neutropenic sepsis.





SIDE EFFECTS OF ACTINOMYCIN-D

More common

- Black, tarry stools
- blood in the urine or stools
- chills
- cough
- diarrhea (continuing)
- difficulty with swallowing
- fever
- heartburn
- hoarseness
- lower back or side pain
- painful or difficult urination
- pinpoint red spots on the skin
- sores in the mouth and on the lips
- stomach pain (continuing)
- unusual bleeding or bruising
- unusual tiredness or weakness

Incidence not known

- Blistering, peeling, or loosening of the skin
- body aches or pain
- chapped, red, or swollen lips
- confusion
- congestion

- cough
- difficulty with breathing
- difficulty with moving
- difficulty with swallowing
- dryness or soreness of the throat
- flushing or redness of the skin
- irregular heartbeat
- joint pain or swelling
- muscle ache, pains, or stiffness
- muscle cramps in the hands, arms, feet, legs, or face
- numbness and tingling around the mouth, fingertips, or feet
- pain at the injection site
- runny nose
- scaling, redness, burning, pain, or other signs of inflammation of the lips
- seizures
- slow growth
- stomach cramps
- swelling of the feet or lower legs
- tender, swollen glands in the neck
- tremor
- unusually warm skin
- voice changes
- yellow eyes or skin

Some side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects.

More common

- Darkening of the skin
- general feeling of discomfort or weakness
- nausea
- skin rash or acne
- unusual feeling of dullness or sluggishness
- vomiting



CONCLUSION

A plan for the diagnosis and treatment of cancer is a key component of any overall cancer control plan. Its main goal is to cure cancer patients or prolong their life considerably, ensuring a good quality of life. In order for a diagnosis and treatment programme to be effective, it must never be developed in isolation. It needs to be linked to an early detection programme so that cases are detected at an early stage, when treatment is more effective and there is a greater chance of cure. It also needs to be integrated with a palliative care programme, so that patients with advanced cancers, who can no longer benefit from treatment, will get adequate relief from their physical, psychosocial and spiritual suffering. Furthermore, programmes should include a awareness-raising component, to educate patients, family and community members about the cancer risk factors and the need for taking preventive measures to avoid developing cancer.

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