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RECOMBINANT ANTIBIOTICS IN CANCER THERAPY- A REVIEW

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Abstract:

Cancer is the disease of uncontrolled cellular growth in which abnormal cells develop and reproduce. Decades of biomedical research in developed nations have resulted in many effective interventions that affect cancer incidence and mortality. The most common cancer treatments are restricted to surgery, conventional chemotherapy and radiotherapy. Although these conventional anticancer therapies are effective in the management of many patients, these therapies are ineffective for approximately half of cancer sufferers. Thus, new strategies are being developed and used to treat cancer by improving, supplementing or replacing conventional methods. Anticancer antibiotics have made a successful impact in the field of chemotherapy. For most of them, DNA is the molecular target. Some act as DNA intercalators or some prevent DNA repair among other mechanism of actions. Some other agents showed that stimulation and enhancement of existing host defense mechanism in one of the additional ways that these chemotherapeutic agents exert their effects.

Keywords:

Cancer, Recombinant therapy, tumour, leukemia, haematopoieic cells, sarcoma.

INTRODUCTION

Cancer is a group of disease which involving abnormal cell growth with the potential to invade or spread to other parts of the body ¹. Cancer being second biggest killer disease and one in three people will be diagnosed with cancer during their life time. Cancer is a leading cause of death in the United States ³. Possible signs and symptoms include lump, bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. Over 100 types of cancers affect humans. Tobacco use is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, lack of physical activity, or excessive drinking of alcohol. Other factors include certain infections, exposure to ionising radiation and environmental pollutants¹.

In 2015, about 90.5 million people had cancer. About 14.1million new cases occur a year. It caused about 8.8 million deaths. The most common type of cancer in male are lung cancer, prostate cancer, colorectal cancer and stomach cancer. In females, the most common types are breast cancer, lung cancer and cervical cancer. In children, acute lymphoblastic leukaemia and brain tumors are most common, except in Africa where non-Hodgkin lymphoma occur more often¹. In the UK, over 365000 new cases were reported and mortality in 2006 was in excess of 154000. Cancer is responsible for approximately one-quarter of all deaths in the UK, with lung and bowel cancer comprising the largest category, closely followed by breast and prostate cancer ².

The risk of cancer increases significantly with age, and many cancers occur more commonly in developed country, nearly 30% of the persons face the risk of developing cancer his life time ^{1,4}. In the developing world, 15% of cancers are due to infections such as Helicobacter pylori, hepatitis B, hepatitis C, human papilloma virus infection, Epstein-Barr virus and human immunodeficiency virus (HIV). Approximately 5-10% of cancers are due to inherited genetic defects from a person's parents ¹.

Cancer can be detected by certain signs and symptoms or screening tests. It is then typically further investigated by medical imaging and confirmed by biopsy. Early detection through screening is useful for cervical and colorectal cancer. The benefits of screening in breast cancer are controversial ¹. There are three main approaches to treating established

cancer – surgical excision, irradiation and drug therapy (often called chemotherapy) and the relative value of each of these approaches depends on the type of tumour and the stage of its development ². Adjuvant chemotherapy and hormonal therapy can extend life and prevent disease recurrence following surgical resection of localized breast, colorectal and lung cancers ⁵.

Pain and symptom management are an important part of care. Palliative care is particularly important in people with advanced disease. The chance of survival depends on the type of cancer and extent of disease at the start of treatment. In children under 15 at diagnosis, the five-year survival rate in the developed world is on average 80%. For cancer in the United States, the average five-year survival rate is 66% ¹.

CANCER

Cancers are a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. They form a subset of neoplasm. A neoplasm or tumour is 'a mass of tissue formed as a result of abnormal, excessive, uncoordinated, autonomous and purposeless proliferation of cells' ⁶. All tumour cells show the six hallmarks of cancer. These characteristics are required to produce a malignant tumour. They include; Cell growth and division absent in the proper signals, Continuous growth and division even given contrary signals, Avoidance of programmed cell death, Limitless number of cell divisions, Promoting blood vessel constructions, Invasion of tissue and formation of metastasis.

SYMPTOMS

- ❖ Any persistent lump or thickening in tissue, especially in the lip and tongue or breast.
- ❖ Unexplained lose of weight.
- ❖ Difficulty in swallowing.
- ❖ Persistent cough or hoarseness.
- ❖ A change in digestive habits.
- ❖ Loss of blood through natural orifice or excess out of date loss of blood in women.

- ❖ Change in color of infected areas (like male wart)
- ❖ A swelling or sore throat that does not heal easily.

CLASSIFICATION

Cancers are classified by the type of cell that the tumour cells resemble and is therefore presumed to be the origin of the tumour. These types include:

Carcinoma: Cancers derived from epithelial cells. This group includes many of the most common cancers and nearly all those in the breast, prostate; lung; pancreas and colon.

Sarcoma: Cancers arising from connective tissues such as bone, cartilage, fat and nerve, each of which develops from cells originating in mesenchymal cells outside the bone marrow.

Lymphoma and Leukemia: These two classes arising from hematopoietic cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.

Germ cell tumour: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary such as seminoma and dygerminoma respectively.

Blastoma: Cancers derived from immature precursor cells or embryonic tissue.

ETIOLOGY OF CANCER

Apart from the malignant tumours of organs The major causes of cancer are;

Chemicals:

Exposure to particular substances has been linked to specific types of cancer. The agents which can induce cancer are called carcinogens. Examples: Tobacco smoke (causes 90% of lung cancer) contains over fifty known carcinogens, including nitrosamides and polycyclic aromatic hydrocarbons. Smoking alone is estimated to have caused 21% of death from cancer worldwide. 5% cancer is attributed to alcohol exposure, especially liver and digestive tract cancer. Cancer from work related – substance exposures may cause between 2 and 20% of cases. Cancer such as lung cancer and mesothelioma can come from inhaling tobacco smoke or asbestos fibers, or leukemia from exposure to benzene ⁶.

Diet and Exercise:

Diet, physical inactivity and obesity are related to upto 30-35% of cancer deaths. Over weight individuals, deficiency of vitamin A and people consuming diet rich rich in animal fats and low in fibre content are more at risk of developing certain cancer like colonic cancer⁶.

Infection:

Worldwide approximately 18% of cancer deaths are related to infectious diseases. Oncovirus include human papillomavirus (cervical cancer), Epstein Barr virus(nasopharyngeal cancer), Kaposi's sarcoma herpesvirus(lymphoma), hepatitis B and hepatitis C viruses(hepato cellular carcinoma) and human T- cell leukemia virus-1(T-cell leukemia).

Radiation:

Upto 10% of invasive cancers are related to radiation exposure, including both ionizing and non-ionizing ultraviolet radiation. Medical use of ionizing radiation is a small but growing source of radiation – induced cancers. Prolonged exposure to UV radiation from sun leads to melanoma.

Heridity:

Hereditary cancers are primarily caused by an inherited genetic defect. Less than 0.3% of the population is carriers of a genetic mutation that has a large effec on cancer risk.

Physical agents:

Some substances cause cancer primarily through their physical, rather than chemical effects. Example: prolonged exposure to asbestos which is a naturally occurring mineral fibre cause mesothelioma. Non-fibrous particulate materials that cause cancer include powdered metallic cobalt, nickel and crystalline silica.

Hormones:

Some hormones play a role in the development of cancer by promoting cell proliferation. Hormones are important agents in sex related cancers, such as cancer of the

breast, endometrium, prostate, ovary and also of thyroid cancer and bone cancer. Osteosarcoma may be promoted by growth hormones ¹.

Autoimmune diseases:

There is an association between celiac disease and an increased risk of all cancers. Rates of gastrointestinal cancers are increased in people with Crohn's disease and ulcerative colitis, due to chronic inflammation. Also, immunomodulators and biologic agents used to treat these diseases may promote developing ex-intestinal malignancies ¹.

Age and Sex:

Generally, cancers occurs in older individuals past 5th decade of life, though there are variations in age incidence in different forms of cancers. Acute leukemias occur in children and in old age group . Apart from the malignant tumours if organ peculiar to each sex, most tumours are generally more common in men than in women except cancer of breast, gall bladder, thyroid and hypopharynx ⁶.

PATHOPHYSIOLOGY OF CANCER

Cancer is fundamentally a disease of tissue growth regulation. In order for a normal cell to transform into a cancer cell, the genes that regulate cell growth and differentiation must be altered.

EPIGENETICS OF CANCER

The classical view of cancer is a set of disease that are driven by progressive genetic abnormalities that include mutations in tumour-suppressor genes and oncogenes and chromosomal abnormalities.

DIAGNOSIS AND SCREENING

Most cancers are initially recognized either because of the appearance of signs or symptoms or through screening. Neither of these leads to a definitive diagnosis, which requires the examination of a tissue sample by a pathologist.

❖ Histological Methods

These methods are based on microscopic examination of properly fixed tissue,

supported with complete clinical and investigative data. These methods are most valuable in arriving at the accurate diagnosis.

❖ **Cytological Methods**

Cytological methods for diagnosis consist of cells shed off into body cavities and study of cells by putting a fine needle introduced under vacuum into the lesion.

❖ **Histochemistry And Cytochemistry**

Histochemistry and cytochemistry are additional diagnostic tools which help the pathologist in identifying the chemical composition of cells, their constituents and their products by special staining methods.

❖ **Immunohistochemistry**

This is an immunological method of recognizing a cell by one or more its specific components in the cytoplasm, cell membrane or nucleus. These cell components (called antigens) combine with specific antibodies on the formalin-fixed paraffin sections or cytological smears. The complex of antigen –antibody on slide is made visible for light microscopical identification by either fluorescent dyes or by enzyme system.

❖ **Electron Microscopy**

Ultra structural examination of tumor cells offers selective role in diagnostic pathology. EM examination may be helpful in confirming or substantiating a tumor diagnosis arrived at by light microscopy and Immunohistochemistry.

A few general features of malignant tumor cells by EM examination are:

- Cell junction – presence and type
- Cell surface e.g. presence of microvilli.
- Cell shape and cytoplasmic extensions.
- Shape of the nucleus and features of nuclear membrane.
- Nucleoli – size and density.

❖ **Tumor markers (Biochemical assays)**

In order to distinguish from the preceding techniques of tumor diagnosis in which 'stains' are imparted on the tumor cells in section or smear, tumor markers or biochemical assays of products elaborated by the tumor cells in blood or other body fluids.

❖ **Modern Aids In Tumor Diagnosis**

In addition to the methods described above, some more modern diagnostic techniques have emerged for pathologic diagnosis but their availability as well as applicability is limited. That are;

- Flow cytometry.
- In situ hybridization.
- Molecular diagnostic techniques.
- DNA microarray analysis of tumours ⁶.

TREATMENT OF CANCER

There are many type of cancer treatment. The type of treatment will depend on the type, location and grade of the cancer as well as the patient's health and preferences. The primary ones include:

- ✓ Surgery
- ✓ Radiation therapy
- ✓ Chemotherapy
- ✓ Immunotherapy
- ✓ Targeted therapy
- ✓ Hormone therapy
- ✓ Stem cell transplant
- ✓ Precision medicine

✓ Palliative care

Surgery

When used to treat cancer, surgery is a procedure in which a surgeon removes cancer from the body. It is the primary method of treatment for most isolated, solid cancers and may play a role in palliation and prolongation of survival. For some type of cancer this is sufficient to eliminate the cancer.

Radiation Therapy

Radiation therapy involves the use of ionizing radiation in an attempt to either cure or improve symptoms. It works by damaging the DNA of cancerous tissue, killing it. The radiation is most commonly low energy x-rays for treating skin cancers, while higher energy x-rays are used for cancers within the body.

Chemotherapy

Chemotherapy is the treatment of cancer with one or more cytotoxic anti-neoplastic drugs (chemotherapeutic agents) as part of a standardized regimen. The efficacy of chemotherapy depends on the type of cancer and the stage.

Immunotherapy

A variety of therapies using immunotherapy, stimulating or helping the immune system to fight cancer. Approaches include antibodies, checkpoint therapy and adoptive cell transfer.

Targeted Therapy

Targeted therapy is a type of cancer treatment that targets the changes in cancer cells that helps them grow, divide and spread.

Hormone Therapy

Hormone therapy is a treatment that slows or stops the growth of breast and prostate cancers that use hormones to grow.

Stem cell Transplant

These are procedures that restore blood-forming stem cells in cancer patients who have had theirs destroyed by very high doses of chemotherapy or radiation therapy.

Precision Medicine

Precision medicine helps doctors select treatments that are most likely to help patients based on a genetic understanding of their disease.

Palliative Care

Palliative care refers to treatment that attempts to help the patient feel better and may be combined with an attempt to treat the cancer. Palliative care includes action to reduce physical, emotional, spiritual and psycho-social distress ¹.

ANTICANCER DRUGS

The anticancer drugs either kill cancer cells or modify their growth. However selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy.

In malignant diseases, drugs are used with the aim of;

- ❖ Cure or prolonged remission

- ❖ Palliation

- ❖ Adjuvant chemotherapy

CLASSIFICATION OF ANTICANCER DRUGS

A. CYTOTOXIC DRUGS

i. Alkylating agents

- Nitrogen mustards: Mechlorethamine, Cyclophosphamide, Ifosfamide, Chlorambusil, Melphalan.

- Ethylenimine : Thio-TEPA

- Alkyl sulfonate : Busulfan
- Nitrosoureas : Carmustine, Lomustine
- Triazine : Dacarbazine, Temozolomide
- Methyl hydrazines : Procarbazine

ii. **Platinum coordination complexes:** Cisplatin, Carboplatin, Oxaliplatin.

iii. **Anti metabolites**

- Folate antagonist : Methotrexate (Mtx), Pemetrexed
- Purine antagonist : 6- Mercaptopurine (6-MP), 6- Thioguanine (6-TG), Azathioprine
- Pyrimidine antagonist: 5- fluorouracil (5-FU), Capecitabine, Cytarabine

iv. **Microtubule damaging agents:** Vincristine, Vinblastine, Paclitaxel, Docetaxel

v. **Topoisomerase- 2 inhibitors:** Etoposide

vi. **Topoisomerase-1 inhibitors:** Topotecan, Irinotecan

vii. **Antibiotics:** Actinomycin D, Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, Bleomycins, Mitomycin.

viii. **Miscellaneous:** Hydroxyurea, L-Asparaginase (LA), Tretinoin, Arsenic trioxide

B. TARGETED DRUGS

i. **Tyrosine protein kinase inhibitors:** Imatinib, Nilotinib

ii. **EGF receptor inhibitors:** Gefitinib, Erlotinib, Cetuximab

iii. **Angiogenesis inhibitors (AI) :** Bevacizumab, Sunitinib

iv. **Unarmed monoclonal antibody (UMA):** Rituximab, Trastuzumab

C. HORMONAL DRUGS

i. **Glucocorticoids :** Prednisolone and others

- ii. **Estrogens:** Fosfestrol, Etinyloestradiol
- iii. **Selective estrogen receptor modulators :** Tamoxifen, Toremifene
- iv. **Aromatase inhibitors:** Letrozole, Anastrozole, Exemestane
- v. **Selective estrogen receptor down regulators :** Fulvestrant
- vi. **Antiandrogen :** Flutamide, Bicalutamide
- vii. **5-alpha reductase inhibitor:** Finasteride, Dutasteride
- viii. **GnRH analogues:** Nafarelin, Leuprolin, Triptorelin
- ix. **Progestins :** Hydroxyprogesterone acetate, etc ⁷.

CYTOTOXIC ANTIBIOTICS

This group of antibiotics derived from the *Streptomyces* species, have prominent antitumor activity.

Mechanism of Action:

- Practically all of them intercalate between DNA strands.
- Interfere with template function.
- Inhibiting DNA and/or RNA synthesis.

I. Actinomycin D

It is a very potent anti neoplastic drug, highly efficacious in Wilm's tumor and childhood rhabdomyosarcoma.

Mechanism of action:

In addition to blocking RNA transcription, it causes single strand breaks in DNA.

Adverse effects:

Vomiting, stomatitis, diarrhea, erythema and desquamation of skin, alopecia and bone marrow depression

II. Daunorubicin, Doxorubicin

These are anthracycline antibiotics having antitumor activity. However, Daunorubicin is limited to acute myeloid as well as lymphoblastic leukaemia, while doxorubicin, in addition, is effective in many solid tumors, such as breast, thyroid, ovary, bladder and lung cancers, sarcomas and neuroblastoma.

Adverse effects:

Marrow depression, alopecia, stomatitis, vomiting and local tissue damage.

III. Epirubicin

This is a recently introduced anthracycline. Epirubicin has been primarily used as a component of for adjuvant therapy of breast carcinoma.

Adverse effects:

Alopecia, hyper pigmentation of skin and oral mucosa, painful oral ulcers, fever and GI symptoms.

IV. Bleomycin

This is a mixture of closely related glycopeptides antibiotics having potent anti tumor activity. It chelates copper or iron, produces superoxide ions and intercalates between DNA strands – cause chain scission and inhibit repair. It is highly effective in testicular tumor and squamous cell carcinoma of skin oral cavity neck and head, genitourinary tract and oesophagus. Also useful in Hodgkin's lymphoma.

Adverse effects:

Mucocutaneous toxicity, pulmonary fibrosis.

V. Mitomycin C

This is highly toxic drug is used only in resistant cancers of stomach, cervix, colon, rectum, breast etc. It is usually combined with 5-FU and radiation. It is transformed intracellularly to a form which act as an Alkylating agent and cross links DNA. It also generates free radicals which damage DNA.

Adverse effect:

Haemolytic-uremic syndrome

VI. Mithramycin

This drug derived from *Streptomyces plicatus*. It has been found to be useful in embryonal cell carcinoma of the testis, in hypercalcemia due to malignant disease and Paget's disease.

Adverse effects:

High toxicity, myelosuppression, thrombocytopenia, liver and kidney damage and bleeding due to suppression of clotting factors ⁷

REVIEW

The study was conducted to 'evaluate the Anti-protozoal and anti-bacterial antibiotics that inhibit protein synthesis kill cancer subtypes enriched for stem cell – like properties'. They show the breast cancer subtypes enriched for stem cell like properties display exacerbated chemical sensitivity to microbicides that target ribosomes and/or inhibit protein synthesis. These findings suggest that classical anti-protozoal and anti-bacterial antibiotics such as emetine, puromycin or acryflavin could be used in combination with currently used conventional cytotoxic chemotherapy in the treatment of breast carcinomas. It is based on the 'cancer therapy using antibiotics' Significant changes in parent chemical structures and newer classes of antibiotics such as their combination can provide a chance for this field to boom again. The newer discovered drugs have hope for more effective drugs in the future and with the growth of drug delivery techniques and newer moieties, control of toxicity will be an achievable task in the near future with these chemotherapeutics. 4-5 different classes of FDA approved antibiotics can be used to selectively target cscs, across multiple tumour types. Doxycycline is relatively attractive as a new anti-cancer agent. The molecular disruption of mitochondrial biogenesis would be a novel therapeutic strategy for the eradication of cscs. This new therapeutic strategy takes advantage of the manageable side effects of these antibiotics, which affect eukaryotic mitochondria.

Dexrazoxane, which is a cardio protective agent for use in conjunction with doxorubicin, has shown the ability to prevent the devastating tissue necrosis after anthracyclines use and hence is the first and only proven antidote in anthracycline extravasation. The combination of oral ciprofloxacin and amoxicillin– clavulanate was as effective as intravenous ceftazidime alone for the empirical management of fever during chemotherapy-induced neutropenia in hospitalized low-risk patients. Treatment was successful in nearly 70 percent of all episodes, regardless of the regimen used. Modifications in the regimens, primarily because of intolerance or insufficient antimicrobial coverage of the study drugs. The most striking difference between the two regimens was that oral therapy was less well tolerated than intravenous therapy. Nonetheless, our finding that the efficacy of the two regimens was equivalent challenges previous assumptions that intravenous delivery of antibiotics is required to achieve a good outcome in patients with fever and neutropenia.

Distamycin an antibiotic is known to specifically target the minor groove of DNA. Another class of compounds, the lexitropins which contain a thiazole moiety and very related to Distamycin has also showed similar modes of action. Mitochondria act as the source of energy and very important for division for the stem cells a crucial process which if goes wrong leads to cancer. These stem cells are strongly associated with the growth and recurrence of all cancers and are especially difficult to eradicate with normal treatment, which also leads to tumour developing resistance to other types of therapy. Mitochondria and bacteria have evolutionary connections and thus some of the antibiotics also affect mitochondria. A few different classes of FDA-approved drugs doxycycline and azithromycin both have been tested and have already shown positive therapeutic effect in cancer patients which opens up another venue for drug discovery.

CONCLUSION

A mass of tissue formed as a result of abnormal, excessive, uncoordinated, autonomous and purposeless proliferation of cells called tumour or neoplasia. This uncontrolled and abnormal cell growth is called cancer. The leading risk factors for death from cancer include smoking, alcohol use, low fruit and vegetable intake, over weight and obesity.

The primary prevention through life style and environmental interventions remains the way to reduce the burden of cancer and also chemo therapeutic agents have greater impact on cancer treatment. The treatment of cancer with one or more cytotoxic anti-neoplastic drugs has a part of standardised regimen. A variety of drugs, which are divided in to broad categories such as cytotoxic, targeted and hormonal drugs are used as chemotherapeutic agents.

Antibiotics as anticancer drugs clearly form an important part of chemotherapeutics with curative properties. Hence control of metastasis and differentiation cannot be achieved effectively by these drugs. The side effects ranging from vomiting, nausea, alopecia, mucotisis, bone marrow suppression to cardio toxicity. New research in the field that Lactoquinomycin derived from medermycine which is an enediyne antibiotics have anti cancer activity. The newer discovered drugs have hope for more effective drugs in the future and with the growth of drug delivery techniques and newer moieties, control of toxicity will be an achievable task in the near future with these chemotherapeutics.

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