ISSN 2581-6217

World Journal of Pharmaceutical Science & Technology

Journal homepage: www.wjpst.com

Review Article

LIFE TRAETENING DISEASE: OVERVIEW

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Received: 15-08-2019, Revised: 25-08-2019, Accepted: 27-08-2019

ABSTRACT

In the last decades, the number of patients receiving chemotherapy has considerably increased. Given the toxicity of cytotoxic agents to humans, the development of reliable analytical methods to analyze these compounds became necessary. The arrival of a great number of new antineoplastic agents has made it necessary to reclassify all of them. Anticancer drugs may act at different levels: cancer cells, endothelium, extracellular matrix, and the immune system or host cells. The tumour cell can be targeted at the DNA, RNA or protein level. Most classical chemotherapeutic agents interact with tumour DNA, whereas monoclonal antibodies and small molecules are directed against proteins. The endothelium and extracellular matrix may be affected also by specific antibodies and small molecules.

KEYWORDS

Antineoplastic, Cytotoxic, Malignancies, Proliferation, Tumour

INTRODUCTION

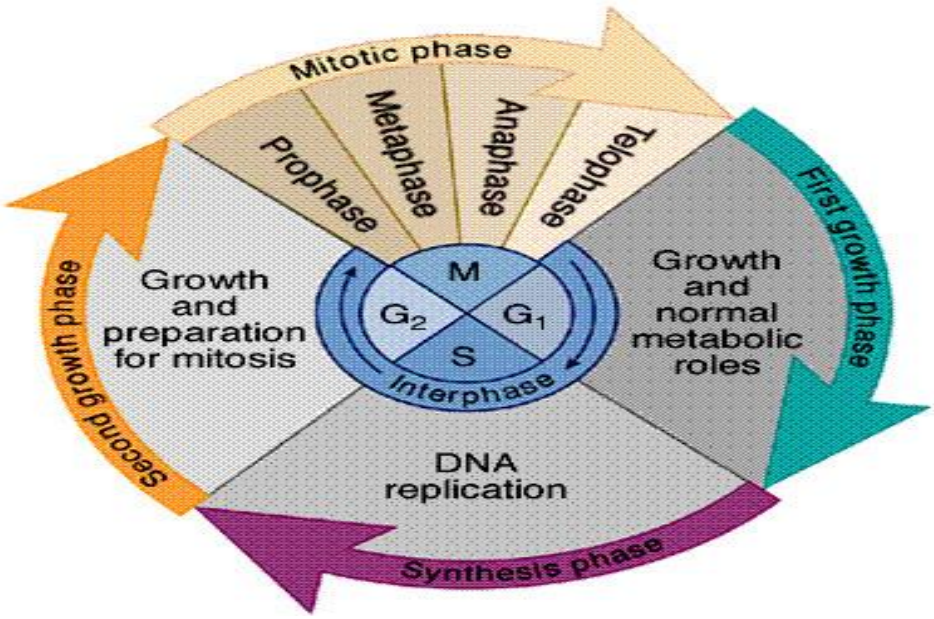
Next to the heart disease, cancer is the major killer of mankind. Irrespective of aetiology cancer is basically a disease of cells is characterized by the loss of normal cellular growth, maturation and multiplication, and thus homeostasis is disturbed. the main features of cancer are (i) Excessive cell growth, usually in the form of tumour; (ii) invasiveness, i.e., the ability to grow into surrounding tissue; (iii)undifferentiated cells or tissues, more similar to embryonic tissues; (iv) the ability to metastasize or spread to new sites and established new growths; (v) a type of acquired heredity in which the progeny of the cancer cells also retains cancereous properties; and (vi) a shift of cellular metabolism towards increased production of macromolecules from nuclieosides and aminom acids,with an increased catabolism of carbohydrates for cellular energy.such a behaviear of cancer cells leads to illeness in the host as result (i) pressure effects due to local tomour growth;(ii) destruction of the organ involved by the primary groeth, orvits metastases; (iii) systemic effects as a result of new growth.[1,2,3,4]

Cancer:

Cancer also called malignancy, s an abnormal growth of cells. there are more than two types of cancer, including Breast cancer, Skin cancer, Colon cancer, Prostate cancer and Lymphoma symptoms vary depending upon the type.

Cell cycle:

Cellular multiplication involves passage of cell trough a cell cycle. the various phases of the cell cycle are characterized as;(1) The interval following cell division to the point where DNA synthesis starts, known as the presynthesis phase,(G1).The variability in the length of the cell cycle between rapidly and slowly replicating cells is accounted by the differences in the length of G1 phase;(2)after mitosis some of the daughter cells passed into a resting phase or non-proliferative phase(G0),and do not re-enter the cell cycle phase immediately. They may enter the G1 phase later. The G0 phase is the sub phase of G1;(3) the DNA synthesis (s) occurs; (4)the premitotic or the post synthesis (G2) phase follows. in this phase RNA and protein synthesis takes place, and it is shorter than the S phase; and (5) lastly mitotic (M) phase follows, In which the synthetic activity of the cell is low, the chromosomes separate into two daughter cells through the subphase-prophase, metaphase, anaphase and telophase. These daughter cells have the option of either entering the G1phase or the G0 subphase of G1phase. [1,2,3]



Most of the antineoplastic drugs act specifically on the processes such as DNA synthesis ,transcription ,or the mitotic phase, and are labelled as cell cycle phase specific drugs(also known phase-dependent drug).the specific drugs do not act on G0 phase .in contrast,there are certain drugs which are kill the cells during all or most phases of the cycle, lablled as cell cycle phase nonspecific drugs (also known as phase-independent drugs). The phase non specific drugs do not possesses a slight effect on the G0 phase.

In general, the cytotoxic drugs can be classified (Bruces classification) according to there effect on the cell cycle. Strictly speaking there is overlapping of activity and activity and the drug at best can be classed as either predominantely phase specific or non-specific.

Cell cycle studies have provided a logical basis for high dosage intermittent combination therapy, which possibly is the most effective mode of treatment. Drugs and timings can be selected to allow maximal tumour cell killing, and minimal emergence of drug resistance. [1,2,3]

The phase specific drugs act chiefly on cells in certain phases, and when in experimental studies a tissue culture is treated with these drugs, the percentage of cells surviving falls rapidly at first with incrasing doses, but reaches a plateau when further increase in dose produces no further increase in dose produces no further increase in cell death. Therefore, the more rapid the cell turnover,the more effective they are. Their dose-response curve is initially exponential, but at higher doses a maximum response is reached and the curve becomes asymptotic. The phase specific drugs have prove effective in haematologic malignancies, and tumours with high rate of proliferation, or high growth fraction. [1,2,3]

Table no 1: Classification of some cytotoxic drugs according to their predominant effect on the cell cycle:

Sr. no	Phase specific drugs	non-specific drugs
	Methotrexate	Nitrogen mustard
	6-mercaptopurine	cyclophosphamide
	5-flurouracil	melphalan
	Cytosine arabinoside	busulphan
	Prednisolone	thio-tepa
	Vincristine	chorambucil
	Vinblastine	actinomycine D
	Procarbazine	adrimycine
	Hydroxyurea	daunomycine
	Asparaginase	mitomycine C

The phase non-specific drugs act on cells in any phase of the cycle, including a slight action on the G0 phase. Cell survival in tissue culture falls progressively with increasing doses. Their dose-response curve follows first-order kinetics, and the cells are killed exponentially with increasing dosage, and the relationship trough out is linear. The non specific drugs, many of which complex with DNA are use full both in the low growth fraction tumors (or solid tumors), and also in some high growth fraction tumor. [1,2,3]

Types of Cancer: [3,4]

- Bladder cancer
- Breast cancer
- Colorectal cancer
- Kidney cancer
- Leukemia
- Lung cancer
- Non Hodgkin lymphoma
- Prostate cancer

Anti-Cancer\Anti-Neoplastic\Anti-Tumour Drug:

Anti-tumour (latin:-tumor swelling neoplasm) drug are used in the treatment of cancer or carcinogen growth is an abnormal mass of new tissue growing in or on part of the body. Several type of carcinogenic regarded to be an in curable disease in secondary stages. The radioactive substances, metal compounds and several chemotherapeutic drugs have been suggested to control the carcinogenic growths

Examples\Clasificastion: [2]

A. Drug Acting Directely On Cells (cytotoxic drugs):

1. Alkylating agents:

   Nitrogen mustard: e.g:-mechlorethamine(mustine HCL),
   Cyclophosphamide,
   Ifosfamide,
   Chorambucil,
   Melphalan

   Ethylenimine: e.g:-Thio-tepa

   Alkyl sulfonate: e.g:-busulfan

   Nitrosoureas: e.g:-carmustine (BCNU),
   Lomustine (CCNU),
   Dacarbazine (DTIC)

2. Antimetabolites:

   Folate antagonist:e.g:-methotrexat

   Purine antagonist:e.g:-6-mercaptopurine(6-MP),
   Azathioprine, Fludarabine

   Pyrimidine antagonist: e.g:- cytarabine

3. Vinca Alkaloid: e.g: Vincristine (oncovin),
   Vinblastin

4. Taxanes: e.g: paclitaxel,
   Docetaxel

5. Epipodophyllo Toxin: e.g: Etoposide

6. Camptothecine Analouges: e.g:- Tropotecan,
   Irinotecan

7. Antibiotics: e.g:- actinomycine D (dactinomycine),
   Doxorubicine,
   Daunorubicine (rubidomycine),
   Mitoxantrone

8. Miscellaneous: e.g:-hydroxyurea,
   Procarbazine,
   L-asparaginase,
   Cisplastine,
   Carboplatine

B. Drugs Altering Hormonal Milieu:-

1. Glucorticoids:-E.G:-Prednisolon And Others
2. Estrogen:-E.Fosfrestol, Ethinylestradiol
3. Selective Estrogen Receptor Modulators:-E.G:-Tamoxiphen, Toremifine
4. Selective Estrogen Receptor Down Regulators:-E.G:-Fulvestrant
5. Aromatase Inhibitors: E.G:- Letrozole, Anastrozole, Exemestane
6. Antiandrogen: E.G:-Flutamide, Bicalutamide
7. 5-A Rectase Inhibitors:E.G:-Finasteride, Dutasteride
8. Gnrh Analouges:E.G:-Nafareline, Triptorelin
9. Progestins:E.G:-Hydroxyprogesteron, Acetate, Etc

Cancer Chemotherapy: [6,7,8]

Drugs Used In Cancer Chemothrearapy:

The main anticancer drugs can be divided into the following general categories.

Cytotoxic Drugs:

The mechanism of action these drugs is discussed more fully below and they include

- alkylating agents and related compounds, which act by forming covalent bonds with DNA and thus impeding replication
- antimetabollites, which block or subvert one or more of the metabolic pathways involved in DNA synthesis
- cytotoxic antibiotics, i.e., substances of microbial origin that prevent mammalian cell division
- plant derivatives9vinca alkaloids,taxanes,campothecins0
- --most of these specifically affect microtubule function and hence the formation of the mitotic spindle.

Hormones, of which the most important are steroids, namely glucocorticoids. oestrogen and androgens, as well as drugs that suppress hormone secretion or antagonize hormone action.

Miscellaneous Agents that do not fit into the above categories. This group includes a number of recently developed drugs designed to affect specific tumour-related target. [9,10,11]

The clinical use of anticancer drugs is the province of the specialist oncologist, who selects treatement regimens appropriate to the patient with the objective of curing,prolonging life or palitative therapy.such matters are not addressed here; instead.we concentrate on more pharmacological matters such as mechanisms of action and the main unwanted effects of commonly used anticancer agents. [12,13,14]

Adverse Effect of Cancer Chemothrapy:

Immediate side effect of chemotherapy is nausea and vomiting. These may be relieved by metoclopramide (10 mg orally or IV), or other antiemetics (chlorpromazine 100n mg orally: prochlorperazine 12.5 mg IV; Domperidone 10 mg iv; Ondansetron 8 mg orally 1-2 hrs before treatement, or 16 mg rectally 1-2 hrs before treatement; or 8 mg IM/slow IV immediately before treatement ; granisetron 1-2 mg orally 1 hrs before treatement, then 2 mg OD or bid during treatement. The delayed adverse effects involve the tissues or systems with a rapid cell turnover rate. [16,18,19]

The main are briefed below:

(a) **Bone marrow depression**. This occurs within 10-14 days after a single dose of a cytotoxic drug, indicated by a fall in circulating leucocytes and platelates. This may lead to bleeding disorders, increased susceptibility to infection, and bone marrow aplasia.

(b) **Gastrointestinal tract**. Bleeding, ulceration and diarrhea may occure.

(c) **Neurotoxicity** . Neuropathy mainly occurs with vinca alkaloids.

(d) **Hepatotoxicity.** This may occure due to the cytotoxic agent itself, or due to its toxic metabolites.

(e) **Teratogenicity and fertility**. Cytotoxic drugs impair fertility, increase of foetal abnormalities, and passibly carcinogenesis. In man these agents can produce a profound reduction in sperm count. In women they do not usually have long term effects.[21]

(f) **Immunosupression.** Parallel to bone marrow depression, these agent exert a direct depressant effect on lymphocytes and other immunocytes. Resistance to microbial infections is lowered, and the immunologic response against the neoplasia is also lowered. Many anticancer drugs (e.g., azathioprine, cyclophosphamide) are used as immunosuppressive agents.

(g) **Superinfection**. As a consequence immunosupression, fungal and other unusual infections may occur, which include invasion by candida albicans, and pneumocystis carnii.[22]

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