

CHEMOTHERAPY

ANTI-CANCER DRUGS

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ANTI-CANCER DRUGS

INTRODUCTION:

The use of drugs to inhibit the rate of growth of, or to kill malignant cells, while having minimal effects on non-malignant host cells, is referred to as cancer chemotherapy

The ideal anti-cancer drug should target malignant cells in preference to non-malignant cells

Selective toxicity of most anti-cancer drugs is based on the accelerated rate of cell division for malignant cells compared to non-malignant cells

ANTI-CANCER DRUGS

INTRODUCTION ... CONT'D:

Anti-cancer drugs currently used include:

- Cytotoxic therapy (which is the main approach)
- Hormonal therapy
- Immunotherapy

Cancers differ in their sensitivity to chemotherapy, from the very sensitive (e.g. lymphomas) where complete clinical cures can be achieved, to the resistant (e.g. non-small cell lung carcinoma)

Adverse effects are very common with anti-cancer drugs and can have a devastating impact on the patient's quality of life

ANTI-CANCER DRUGS

LEARNING OBJECTIVES:

1. To outline the goals of cancer treatment
2. To describe the general principles of cancer treatment
3. To classify anti-cancer drugs
4. To describe the salient pharmacological features of selected anti-cancer drugs, including their indications and adverse effects

ANTI-CANCER DRUGS

General Principles

GOALS OF CANCER TREATMENT

Primary goal

Cure the patient i.e. eradicate the cancer (render the patient clinically and pathologically free of disease and return their life expectancy to that of healthy individuals of the same age and sex)

Current therapies do not offer cures for all patients

The best alternative goal

To prolong survival while maintaining the patient's functional status and quality of life (amelioration of symptoms and preservation of quality of life, while striving to extend life)

GOALS OF CANCER TREATMENT ... CONT'D

The third goal

Relieve symptoms such as pain for patients in whom the likelihood of cure or prolonged survival is very low

MODALITIES OF CANCER THERAPY

The major modalities of therapy are

1. Surgery (for local and local-regional disease)
2. Radiation therapy (for local and local-regional disease)
3. Chemotherapy (for systemic disease)

Other important methods include

- Hormonal therapy (for selected cancers, e.g. prostate, breast, endometrium)
- Biologic therapy: immunotherapy (monoclonal antibodies, interferons, and other biologic response modifiers and tumor vaccines)

PRINCIPLES OF CANCER TREATMENT

The most appropriate type of therapy for each individual patient is determined by

- Type and extent of tumor involvement
- Treatment goals
- Performance status
- Age
- Concomitant disease

PRINCIPLES OF CANCER TREATMENT

CONT'D

The modalities often used in combination based on patient and tumour characteristics, as well as patient preferences

- Surgery and radiation therapy as “local treatments”(though their effects can influence behavior of tumor at remote sites
- Chemotherapy and biologic therapy as “systemic treatments”

CANCER CHEMOTHERAPY

- Cancer chemotherapy is limited in case of primary localized cancer, since only a few solid tumors are sensitive enough to be treated with drugs alone
- Chemotherapy is the main treatment in disseminated cancer, because drugs go almost everywhere in the body

CANCER CHEMOTHERAPY ... CONT'D

Chemotherapy cannot reach these areas:

1. Central nervous system
2. Testes
3. Ovaries

Chemotherapy cannot penetrate these sites well and they can act as sanctuary sites for tumor cells i.e. tumor cells in these sites are protected from the effects of circulating chemotherapy drugs

USES OF CANCER CHEMOTHERAPY

Primary chemotherapy

Chemotherapy is used as the sole anti-cancer treatment in a highly sensitive tumor types (e.g. cyclophosphamide-doxorubicin-vincristine-prednisolone for Non-Hodgkins lymphoma)

Adjuvant chemotherapy

Treatment is given after surgery to “mop up” microscopic residual disease (e.g. doxorubicin and cyclophosphamide for breast cancer)

USES OF CANCER CHEMOTHERAPY ...

CONT'D

Neo-adjuvant chemotherapy

Treatment is give before surgery to shrink tumor and increase chance of successful resection (e.g. doxorubicin and ifosfamide for osteosarcoma)

Concurrent chemotherapy

Treatment is given simultaneous to radiation to increase sensitivity of cancer cells to radiation (e.g. cisplatin, 5-fluourouracil and radiotherapy for head and neck tumors)

CHEMOTHERAPY IN DISSEMINATED CANCER

Disseminated or systemic cancer includes several situations:

1. Cancers that by their nature are considered widespread from the time of diagnosis i.e. most hematological malignancies such as leukemias and lymphomas. Chemotherapy in this case is used as primary treatment and is given with the intent to cure or prolong life.
2. Cancers with evident metastatic spread: cancers in this case are very rarely cured and chemotherapy is administered with the goal of prolonging life or reducing symptoms
3. Cancers that appear localized but have developed clinically undetectable micro metastases. Systemic therapy attempts to eradicate these micro tumors and increase cure rate following surgery or radiation.

CHEMO-SENSITIVITY OF TUMOURS

High

Choriocarcinoma

Acute lymphocytic
leukaemia

Hodgkin's
disease

Non-Hodgkin's
lymphoma

Testicular cancer

Small cell lung
carcinoma

Wilms' tumour

Medium

Ovarian cancer

Breast cancer

Osteosarcoma

Head & neck
cancer

Multiple myeloma

Bladder cancer

Colorectal cancer

Low

Non-small cell lung
carcinoma

Cervical cancer

Endometrial cancer

Adult soft tissue
sarcoma

Malignant melanoma

Liver cancer

Pancreatic cancer

Prostate cancer

Gastric cancer

NEOPLASMS IN WHICH CHEMOTHERAPY IS THE PRIMARY THERAPEUTIC MODALITY FOR LOCALIZED TUMORS

- Large cell lymphomas
- Burkitt's lymphoma
- Childhood and some adult stages of Hodgkin's disease
- Wilms' tumor
- Embryonal rhabdomyosarcoma
- Small cell lung cancer
- Central nervous system lymphomas

NEOPLASMS IN WHICH PRIMARY CHEMOTHERAPY CAN ALLOW FOR LESS MUTILATING SURGERY

- Anal carcinoma
- Bladder carcinoma
- Breast cancer
- Laryngeal cancer
- Osteogenic sarcoma
- Soft tissue sarcomas

NEOPLASMS IN WHICH CHEMOTHERAPY IS BE USED FOR METASTASES AND/OR WIDESPREAD DISEASE

- Embryonal carcinoma
- Choriocarcinoma
- Non-Hodgkin's lymphoma
- Leukemias (acute lymphoblastic leukemia, acute myeloid leukemia)

CANCER CHEMOTHERAPY STRATEGY

- The ideal chemotherapeutic drug should target and destroy only cancer cells (however, only few such drugs exist)
- For each patient, drug toxicity is weighed against likelihood of benefit
- Monotherapy is rarely used (however, it may be curative for certain cancers, e.g. methotrexate for choriocarcinoma)

CANCER CHEMOTHERAPY STRATEGY ... CONT'D

Combination therapy:

- Provides maximal cell kill within tolerable toxicity
- Provides broader range of coverage of resistant cells in a heterogeneous tumor
- Prevents/slows the development of drug resistant cells

Multi-drug regimens can provide significant cure rates with certain malignancies such as acute leukaemias, lymphomas, Hodgkin's disease and testicular cancer

COMBINATION CHEMOTHERAPY

The combinations should include:

- Drugs effective in a particular malignancy
- Drugs with different mechanisms of action
- Drugs with non-overlapping toxicity
- Drugs with different patterns of resistance

The drugs should be used in their optimal dose and schedule and should be given at consistent (and as short as possible) intervals

MECHANISMS OF ACTION OF CYTOTOXIC DRUGS

- Inhibition of DNA and RNA synthesis
- Disruption of DNA structure and function
- Inhibition of protein synthesis
- Inhibition of microtubule function

MECHANISMS OF ACTION OF ANTI-CANCER DRUGS

Mechanism of action	Drugs acting by this mechanism
Alkylation of DNA (covalent bond formation) thus interfering with the structure and function of DNA	Alkylating agents: mechlorethamine, cyclophosphamide, melphalan, chlorambucil, busulfan, carmustine, lormustine, dacarbazine
Intercalation with DNA thereby blocking synthesis of DNA and RNA	Dactinomycin (actinomycin D), doxorubicin, daunorubicin and epirubicin
Inhibition of mitosis	Binding on tubulin thereby inhibiting polymerization of microtubules: vinca alkaloids (vincristine, vinblastine and vinorelbine Disassembly of microtubules: paclitaxel and docetaxel

MECHANISMS OF ACTION OF ANTI-CANCER DRUGSCONT'D

Mechanism of action	Drugs acting by this mechanism
Inhibition of topo-isomerase I resulting in DNA damage	Topotecan and irinotecan
Inhibition of topo-isomerase II resulting in double stranded DNA breaks	Etoposide
Inhibition of nucleic acid synthesis by competing with normal metabolites	Anti-metabolites: methotrexate (dihydrofolate reductase inhibitor), cytarabine, fluoro-uracil, capecitabine and gemcitabine (pyrimidine antagonists) 6-mercaptopurine and 6-thioguanine (purine antagonists)
DNA chain scission and fragmentation	Bleomycin

MECHANISMS OF ACTION OF ANTI-CANCER DRUGS ... CONT'D

Mechanism of action	Drugs acting by this mechanism
Cross-linking of DNA subunits with resultant inhibition of DNA synthesis	Platinum compounds (cisplatin, carboplatin and oxaliplatin)
Chromosomal breaks with inhibition of DNA, RNA and protein synthesis	Procarbazine
Inhibition of ribonucleotide diphosphate reductase thereby inhibiting formation of deoxyribonucleotides	Hydroxyurea

MECHANISMS OF DRUG RESISTANCE WITH ANTI-CANCER DRUGS

- Alteration of drug target
- Development of alternative pathways
- Drug inactivation by tumour cells
- Defective apoptosis in tumour cells
- Loss of receptors for hormonal drugs
- Development of cell membrane transporters that cause efflux of the drugs
- Decreased uptake of drug in tumour cells

CANCER CHEMOTHERAPY TOXICITY

- Adverse effects are very common with anti-cancer drugs
- Therapeutic effects of anti-cancer drugs are usually achieved by killing actively growing cells, which are most sensitive to cytotoxic drugs
- Because normal cells and cancer cells have similar sensitivity to chemotherapeutic agents, adverse effects are mostly seen in normally dividing non-neoplastic cells such as bone marrow stem cells, gastric and intestinal mucosa, skin, mucous membranes and hair follicles

COMMON ADVERSE EFFECTS WITH CYTOTOXIC DRUGS

- Bone marrow suppression: Anemia, neutropenia, thrombocytopenia, immunosuppression
- Skin/mucosa: Scaling, mucositis, mucosal haemorrhage, alopecia
- Cardiac: Decreased myocardial contractility, arrhythmias
- Renal: Acute tubular necrosis, chronic renal insufficiency, hemorrhagic cystitis,
- Neurologic: Hearing loss, peripheral neuropathy

COMMON ADVERSE EFFECTS WITH CYTOTOXIC DRUGS ... CONT'D

- Reproductive system: Sterility (reduced spermatogenesis and amenorrhoea)
- GIT: Nausea/vomiting, diarrhea, mucositis, xerostomia, oral mucosal infections
- Dental: Dental pulp/periapical infections, periodontal infection, odontogenic pain
- Osteonecrosis
- Teratogenicity
- Carcinogenicity

ANTI-CANCER DRUGS THAT CAUSE LITTLE OR NO BONE MARROW DEPRESSION

- Hormones
- Vincristine
- Bleomycin
- L-asparaginase
- Cisplatin

SPECIFIC ANTI-CANCER DRUGS

COMMONLY USED ANTI-CANCER DRUGS

Drug	Commonly responsive cancers	Mechanism of action
Cyclophosphamide Chlorambucil	Leukemias, Hodgkin's lymphoma	Alkylation of DNA resulting in DNA strand breakage
Mechlorethamine	Lymphomas	
Methotrexate	Choriocarcinoma, acute leukemias	Folate antagonist: inhibits conversion of DHF to THF – inhibits DNA synthesis
6-Mercaptopurine	Choriocarcinoma, acute leukemias	Purine antagonist: inhibits DNA synthesis

COMMONLY USED ANTI-CANCER DRUGS

CONT'D

Drug	Commonly responsive cancers	Mechanism of action
5-Fluorouracil	Carcinoma of the stomach, colon, rectum, breast and ovaries	Pyrimidine antagonist: inhibits DNA synthesis
Daunorubicin	Acute leukemias	Inhibit DNA synthesis
Doxorubicin	Leukemias, solid tumours	
Actinomycin D (Dactinomycin)	Wilm's tumour, rhabdomyosarcoma, choriocarcinoma	Inhibits RNA synthesis

COMMONLY USED ANTI-CANCER DRUGS

CONT'D

Drug	Commonly responsive cancers	Mechanism of action
Vincristine	Lymphomas, leukemias, Wilm's tumour, brain tumour	Arrest mitosis by inhibiting polymerization of microtubules
Vinblastine	Testicular tumours, Ewing's sarcoma, breast cancer, lymphomas, leukemias	
Vinorelbine	Lung and breast cancer	
Paclitaxel Docetaxel	Breast, ovarian, lung, head and neck, and bladder cancer	Arrest mitosis

COMMONLY USED ANTI-CANCER DRUGS ...

CONT'D

Drug	Commonly responsive cancers	Mechanism of action
Etoposide	Testicular and lung cancers	Inhibit topoisomerase and result in DNA strand breakage
Procarbazine	Hodgkin's lymphoma	Damages DNA
L-Asparaginase	Acute leukemias	Convert asparagine to aspartate depriving malignant cells of asparagine thereby inhibiting protein synthesis
Cisplatin	Ovarian, testicular, and head and neck cancers	Inhibits DNA synthesis

SPECIFIC ADVERSE EFFECTS OF SOME ANTI-CANCER DRUGS

Drug	Specific adverse effects	Other prominent adverse effects
Cyclophosphamide	Haemorrhagic cystitis, stomatitis	Myelosuppression, alopecia, vomiting, amenorrhoea, teratogenicity, secondary leukemias
Methotrexate (toxicity is treated with folinic acid)	Nephrotoxicity, hepatotoxicity, acute pneumonitis, pulmonary fibrosis	Myelosuppression, mucositis, GI disturbances, alopecia, headache, teratogenic
Vincristine	Neurotoxicity, peripheral neuritis, mental depression	Muscle weakness, alopecia
Busulfan	Pulmonary fibrosis, stomatitis	Myelosuppression, alopecia, vomiting, amenorrhoea, teratogenicity

SPECIFIC ADVERSE EFFECTS OF SOME ANTI-CANCER DRUGS ... CONT'D

Drug	Specific adverse effects	Other prominent adverse effects
Cisplatin	Ototoxicity	Highly emetogenic, renal dysfunction
Bleomycin	Pulmonary fibrosis, oedema of hands	Stomatitis, alopecia
Daunorubicin Doxorubicin	Cardiotoxicity (daunorubicin also causes red coloured urine)	Myelosuppression, alopecia
Mitotane	Dermatitis, mental depression	Diarrhoea
Aspariginase	Pancreatitis, hepatotoxicity	Allergic reactions

HORMONAL THERAPY

Option for management of cancers from tissues whose growth is under gonadal hormonal control, especially breast, prostate, and endometrial cancers

These cancers may regress if the "feeding" hormone is eliminated or antagonized.

Major organ system toxicity is uncommon from hormonal treatment, making it the least toxic of systemic anticancer therapies

Uses of hormonal therapy

- As adjuvant therapy
- To treat disseminated disease

HORMONAL THERAPY ... CONT'D

Modes of hormonal therapy:

1. Hormone deprivation

- Removal of hormone producing tissue (ablation)
- Inhibition of hormone production
- Blocking of hormone receptors

2. Exogenous hormone treatment

EXAMPLES OF CANCERS WHERE HORMONAL THERAPY IS USED

- Breast cancer
- Prostate cancer
- Endometrial cancer
- Renal cancer
- Ovarian cancer

HORMONE THERAPY FOR BREAST CANCER

- Hormone therapy may be used to prevent the growth, spread, and recurrence of breast cancer
- Estrogen can increase the growth of breast cancer cells in some women
- Hormone therapy may be considered for women whose breast cancers test positive for oestrogen and progesterone receptor

HORMONE THERAPY FOR BREAST CANCER CONT'D

Hormone therapy for breast cancer includes the following:

1. Estrogen source ablation (oophorectomy and adrenalectomy)
2. Removal or inhibition of gonadotropin action
3. Estrogen receptor blocking: tamoxifen and fulvestrant (estrogen receptor antagonists)
4. Inhibition of peripheral estrogen synthesis: aromatase inhibitors (anastrozole, exemestane, letrozole) which block conversion of androgen to estrogen

HORMONAL THERAPY OF BREAST CANCER CONT'D

Removal or inhibition of gonadotropin action

- Hypophysectomy (removal of pituitary gland)
- GnRH agonists (e.g. goserelin, buserelin, leuprolide): inhibit gonadotrophin synthesis on continuous administration
- GnRH antagonists (e.g. degarelix): inhibit release of GnRH and gonadotrophins
- Progestogens (e.g. megestrol acetate): inhibit gonadotrophin secretion

HORMONAL THERAPY OF PROSTATE CANCER

Options available include:

- Orchiectomy
- Oestrogens (diethylstilbestrol): inhibit effects of endogenous androgens
- Androgen receptor antagonists: flutamide, bicalutamide, nilutamide and cyproterone

HORMONAL THERAPY OF PROSTATE CANCER: OPTIONS AVAILABLE ... CONT'D

- Gonadotrophin-releasing hormone (GnRH) agonists: When given continuously, they inhibit gonadotrophin synthesis and thus reduce synthesis of testosterone. GnRH agonists used in the treatment of prostate carcinoma include leuprolide , goserelin, triptorelin, histrelin, and buserelin
- GnRH receptor antagonists: Inhibit gonadotrophin synthesis and thus lower testosterone (usually more rapidly than GnRH agonists). The GnRH antagonist used in prostate carcinoma is degarelix.

GLUCOCORTICOIDS

Glucocorticoids are lymphocytotoxic and anti-mitotic

They are useful in malignancies in which lymph tissue is involved

Prednisolone and methylprednisolone are used as part of cancer treatment regimens in the following:

- Acute lymphocytic leukemia
- Chronic lymphocytic leukemia
- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Multiple myeloma

BIOLOGICAL THERAPIES

Biological therapies boost the immune system, either directly or indirectly by

- Making cancer cells more recognizable by the immune system, and more susceptible to destruction
- Boosting the killing power of immune system cells
- Changing the way cancer cells grow, so that they act more like normal cells

MECHANISMS OF BIOLOGICAL THERAPIES

.... CONT'D

- Stopping the process that changes a normal cell into a cancerous cell
- Enhancing the body's ability to repair or replace normal cells damaged or destroyed by other forms of cancer treatment, such as chemotherapy or radiation
- Preventing cancer cells from spreading to other parts of the body

ROLE OF THE IMMUNE SYSTEM IN CONTROL OF MALIGNANCY

The immune system is an effective anti-tumour defense

- Malignant cells occasionally arise in healthy bodies as a result of mutations but not all these cells give rise to clinically evident cancer
- There are rare cases of spontaneous remission from metastatic cancer
- An intact immune system can identify malignant cells and destroy them without negative effects on normal cells

Immunotherapy is therefore an important type of biological therapy in the management of cancer

IMMUNOTHERAPY

Examples of immune therapies used in cancer treatment:

- Cytokines (interferons and interleukins)
- Cytokine modifiers (thalidomide and lenalidomide)
- Tumour vaccines
- Antibodies

INTERFERONS (IFNS)

- IFNs are biological response modifiers (BRMs) that occur naturally in the body (BRMs change the way the body's defenses interact with cancer cells and boost the body's ability to fight the disease)
- IFNs have been shown to improve the way a cancer patient's immune system acts against cancer cells
- IFNs may work directly on cancer cells to slow their growth
- IFNs may cause cancer cells to change into cells with more normal behavior
- Some IFNs may also stimulate natural killer cells, T cells, and macrophages

CYTOKINES ... CONT'D

Interleukins

- Interleukins are cytokines that occur naturally in the body
- They stimulate the growth and activity of immune cells, such as lymphocytes, which work to destroy cancer cells

Examples of cytokines used in cancer treatment

- Interferon alfa-2b: hairy cell leukemia and Kaposi's sarcoma
- Interleukin-2: metastatic kidney cancer and melanoma

CYTOKINE MODIFIERS

Include thalidomide and lenalidomide

Mechanism of action: Enhance T-cell production of cytokines (IL-2, IFN- γ) and enhance NK cell-mediated cytotoxicity against tumour cells

Indications: Brain tumors, Kaposi's sarcoma and multiple myeloma

MONOCLONAL ANTIBODIES (MoABs)

- MoABs consist of immunoglobulin sequences that are known to recognize a specific antigen or protein on the surface of cells
- Two main classes of MoABs are used in the treatment of cancer
 1. Unconjugated or naked MoABs
 2. Immunoconjugates: MoABs conjugated to a toxin (immunotoxin), chemotherapy agent, or radioactive particle (radioimmunoconjugate)

MONOCLONAL ANTIBODIES CONT'D

Unconjugated MoABs

Target antigens on the cell surface of cancer cells and directly mediate cell killing. Examples include:

- Alemtuzumab (used in chronic lymphocytic leukemia treatment)
- Trastuzumab (used in treatment of HER-2 positive breast cancer)

MONOCLONAL ANTIBODIES CONT'D

Immuno-conjugates

Deliver a chemotherapy drug or radioactive particle to the site of disease. Once bound to target antigens, the chemotherapy drug conjugated to the MoAB is internalized by the target cell and kills tumor cells through traditional mechanisms of action. Examples include:

- Britumomab used in the treatment of lymphomas (delivers radiation)
- Ado-trastuzumab emtansine: Trastuzumab is chemically linked to the cytotoxic drug, emtansine (used in treatment of HER-2 positive breast cancer)

END