Anticancer drugs

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Classification of anticancer drugs

- Antimetabolites
- Antibiotics
- Alkylng agents
- Microtubule inhibitors
- Steroid Hormones and their antagonists
- Aromatase inhibitors
- Monoclonal antibodies

Antimetabolites

Methotrexate

5-Fluorouracill

6-Mercaptopurine

Methotrexate

Mechanism of action:

Methotrexate causes inhibition of dihydrofolatable reductase and reduction to the tetrahydrofolate form. This leads to depressed DNA, RNA and protein synthesis and ultimately to cell death.

Therapeutic uses:

Methotrexate, usually in combination with other drugs, is effective against acute lymphocytic leukemia, choriocarcinoma, breast cancer, Burkitt lymphoma in children and head and neck carcinomas.

Adverse effects:

- nausea, vomiting, diarrhea
- rash, urticaria
- alopecia
- renal damage
- hepatic function

Contraindications

Methotrexate is teratogenic and should be avoided in pregnancy

5-Fluorouracil

Mechanism of action:

It blocks Thymidylate synthetase and may cause needed for DNA synthesis and cell growth.

Therapeutic uses:

5- Fluorouracil is also effective for the treatment of superficial basal cell carcinomas of some patients with colon cancer.

Adverse effects of 5-Fluorouracil:

- nausea, vomiting, diarrhea
- alopecia
- bone marrow depression
- dermopathy (erythematous desquamation of the palms and soles) colled the “hand-foot syndrome”

6-Mercaptopurine

Mechanism of action:

It is the analog hypoxanthine.

It must penetrate target cells of leukemia

6-mercaptopurine-ribose- phosphate and inhibits

the first step of the de novo purine-ring biosynthesis.

This results is nonfunctional RNA and DNA.

Therapeutic uses:

6-Mercaptopurine is used principally in the maintenance of remission in acute lymphoblastic leukemia.

Adverse effects:

- nausea, vomiting, diarrhea
- alopecia
- bone marrow depression

Antibiotics

Doxorubicin

Doxorubicin is classified as anthracycline antibiotics. Doxorubicin is one of the most important and widely used anticancer drugs.

Mechanism of action:

Doxorubicin may cause intercalation in the DNA.
The drug inserts nonspecifically between adjacent
base pairs and binds to the phosphate backbone of DNA.
This causes local uncoiling and thus blocks DNA
and RNA synthesis.
Intercalation can interfere with the topoisomerase II
–catalyzed breakade/reunion reaction of DNA stands,
causing irreparable breaks.

Doxorubicin is interacts with molecular oxygen producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA.
Lipid peroxidation therefore may explain the *cardiotoxicity* of anthracyclines.

Therapeutic uses:

Doxorubicin is used in combination with other agents for treatment of carcinomas, including breast and lung, acute lymphocytic leukemia and lymphomas.

Adverse effects:

- alopecia
- bone marrow depression
- stomatitis and G.I. tract disturbances
- irreversible, dose-dependent cardiotoxicity (as a result of the generation of the free radicals and lipid peroxidation)

Alkylating agents

Cyclophosphamide

It is the most commonly used alkylating agent. It alkylates the 7 nitrogen of a guanine residue in one or both strands of a DNA molecule. Alkylation of guanine bases in DNA is responsible for the cytotoxic effect of cyclophosphamide, especially those in G_1 and S phases.

Therapeutic uses:

Cyclophosphamide is effective against Burkitt lymphoma and breast cancer

Adverse effects:

- bone marrow depression
- nausea, vomiting
- immunosupression

Microtubule inhibitors

Vinblastine

Vinblastine is vinca alkaloid – alkaloid from plant Vinca rosea

Mechanism of action:

Vinblastine is cell cycle-specific and phase-specific, because it blocks mitosis in metaphase. It bindings to the microtubular protein tubulin, is GTP-dependent and blocks the ability of tubulin to polymerize to form microtubules.

The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation.

Therapeutic uses:

Vinblastine is generally administered in combination with other drugs.

It is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, Hodgkin and non-Hodgkin lymphomas, as well as some other rapidly proliferating neoplasms.

Adverse effects:

- bone marrow depression
- nausea, vomiting, diarrhea
- flebitis
- Alopecia
- Whereas peripheral neuropathy (paresthesias, loss of reflexes, footdrop and ataxia)

Steroid Hormones and their antagonists

Prednisone

Mechanism of action:

Prednisone itself is inactive, and must first be reduced to prednisolone by 11-B- hydroxysteroid dehydrogenase. This steroid then binds to a receptor that triggers the production of specific proteins.

Therapeutic uses:

Prednisone is a potent, synthetic anti-inflammatory corticosteroid. It may cause lymphocytopenia and decreased lymphoid mass.

Adverse effects of Prednisone:

- immunosuppressant action
- peptic ulcers
- hyperglycemia
- cataract formation, glaucoma
- osteoporosis
- euphoria or psychosis
- other adverse effects associated with glucocorticiods

Estrogens

Ethinyl estradiol

Mechanism of action:

Ethinylestradiol inhibits the growth of prostatic tissue by blocking the production of LH, thereby decreasing the synthesis of androgens in the testis. Thus, tumors that are dependent on androgens are affected.

Therapeutic uses:

Estrogens had been used in the treatment of prostatic cancer.

Adverse effects of estrogens:

- tromboemboly
- myocardial infarction
- strokes
- hypercalcemia

Flutamide

It is synthetic, nonsteroidal antiandrogens

Mechanism of action:

Flutamide complets with the natural hormone for binding to the androgen receptor and prevent its translocation into the nucleus.

Therapeutic uses:

Flutamide may be used in the treatment of prostate cancer.

Adverse effects:

- gynecomastia
- G.I. distressand
- liver failure

Tamoxifen

It is an estrogen antagonist.

Mechanism of action:

Tamoxifen binds to the estrogen receptor, but the complex is not productive. The result is a depletion of estrogen receptors, and the growth-promoting effects of the natural hormone and other growth factors are suppressed.

Therapeutic uses:

Tamoxifen is used for first-line therapy in the treatment of estrogen receptor-positive breast cancer in premenopausal women.

Adverse effects:

- nausea, vomiting
- skin rash
- vaginal bleeding
- tromboemboly

Megestrol acetate

It was formerly the progestin used most widely in treating metostatic hormone-responsive breast and endometrial neoplasms.

Goserelin

It is gonadotropin-releasing hormone (GnRH). It is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones, leuteinizing hormone (LH) and folliclestimulating hormone (FSH).

Mechanism of action:

As GnRH agonist, it occupys the GnRH receptor in the pituitary, which leads to its desensitization and consequently, inhibition of FSH and LH.
Thus, both androgen and estrogen syntheses are reduced with regression of tumor and relief of bone pain.

Therapeutic uses:

Goserelin yas some benefit in premenopausal women with advanced breast metastatic carcinoma of the prostate

Adverse effects:

- Impotence
- hot flashes

Aromatase inhibitors

Anastrozole

The aromatase reaction is responsible for the extra-adrenal synthesis of estrogen from androstenedion, which takes place in liver, fat, muscle, skin and breast tissue, including breast malignancies.

Peripheral aromatization is an important source of estrogen in postmenopausal women.

Aromatase inhibitors decrease the production of estrogen in these women.

Therapeutic uses:

Anastrozole has gained favor in the treatment of breast cancer because it is more potent, more selective than other drugs.

Adverse effects:

- nausea
- fatigue
- hot flashes
- acne and hair changes

Monoclonal antibodies

Trastuzumab
Rituximab

Monoclonal antibodies have become an active area of drug development for anticancer therapy because they are directed at specific targets, and often have fewer adverse effects.

Trastuzumab

It is a recombinant DNA-produced, humanized monoclonal antibody, specifically targets the extracellular domain of the HER2 growth receptor that has intrinsic tyrosine kinase activity.

Mechanism of action:

Trastuzumab binds to HER2 sites in breast cancer tissue and inhibits the priliferation of cells that overexpress the HER2 protein, thereby deckreasing the number of cells in the S phase.

Spectr of the activity of Trastuzumab:
metastatic breast cancer, overexpression of transmembrane human epidermal growth factor-receptor 2 (HER2).

Adverse effects:

- congestive heart failure (the most serious toxicity)
- fever and chills
- headache, dizziness
- nausea, vomiting, abdominal pain

Rituximab

It is monoclonal antibody directed against the CD20 antigen on the surfaces of normal and malignant B lymphocytes.
CD20 plays a role in the activation process for cell-cycle initiation and differentiation.

Mechanism of action:
Rituximab has proven to be effective in the treatment of post-transplant lymphoma and chronic lymphocyticleukemia.

Adverse effects of Rituximab:

- hypotension
- bronchospasm
- angioedema
- acute renal failure
- cardiac arrhythmias
- leukopenia, thrombocytopenia, neutropenia
- hyperkalemia, hypocalcemia, hyperuricemia


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