Alkylating agents: -

these agent produce damage to growing and multiplying cells. These drugs produced immunosuppressant effect. Act by alkylating DNA. The most common site of alkylation is N-7 position of guanine. The alkylating agent appear to be the most effective on G1 or S phase. Highly reactive agent can alkylate or bind covalently with cellular components of DNA.

Adverse effect: - leucopenia, anaemia, thrombocytopenia, nausea, vomiting.

Therapeutic use of different alkylating agent can be summarized as fellow:-

1. **Mechlorethamine**: - it is nitrogen mustard, very reactive given to patient in I.V form. Useful in hodgkin's disease.

Dose; - 0.4 mg/kg I.V in 1-4 days. Dose may be repeated after 6 weeks if bone marrow function are not affected.

2. **Cyclophosphamide (Endoxan**):- it is inactive compound but is activated in the liver. It bind to DNA and destroys the cancer cells. It is broad spectrum antitumour drug and has prominent immunosuppressant properties. It can be given orally, I.V, I.M and I.P. it is used for leukaemia, hodgkin's disease, breast cancer, lymphomas

Dose:- 2-3 mg/kg/day for 7 to 10 days orally. Can be given in higher dose if required.

3. **Ifosfamide** :- it has longer action. It is used for breast,testicular, badder, head and neck cancer.

4. **Chlorambucil (Leukeran)**:- it is slow acting alkylating agent and is a drug of choice for long term maintainace of chronic lymphocytic leukaemia and Hodgkin disease. It is effective orally and completely metabolised.

Dose:- 4-10 mg daily for 3-6 weeks and then maintain 2 mg daily.

5. **Melphalan:**- very effective in multiple mmyeloma and breast cancer, effective orally.

Dose 4-6 mg daily for 7 days

Adverse effect:- bone marrow depression.

ANTIMETABOLITES

It prevents the biosynthesis of normal cellular metabolites. Inhibits essential components of cell synthesis by competing with the natural substrate for enzyme involved in synthesis of cell components.

Folic acid antagonist

1. **Methotrexate: -** It is folic acid analogue. Folic acid is essential for the production of tetrahydrofolate. Tetrahydrofolate is essential for synthesis of proteins and pyrimidine. Methotrexate kills cells in S shaped by inhibiting DNA synthesis and prevent cell-division. It absorbed orally and excreted unchanged in urine.

Dose:- 2.5 -10 mg daily orally or 30 mg/kg once a month

Uses :- in acute lymphoblastic leukaemia, cancer of breast, tongue, pharynx.

Adverse effect:- anaemia, thrombocytopenia, leucopenia, bone marrow depression, intestinal ulceration, dermatitis, nephrotoxicity, hepatotoxicity.

Pyrimidine analogs :- these agents inhibit synthesis of pyrimidine (Cytosine and thymine)

1. **5-Flurouracil (5-FU)**:- it is a pyrimidine antagonist. It inhibit DNA synthesis.

Uses:- fluorouracil is useful in hepatoma, adrenocarcinoma of git, carcinoma of breast, cervix of uterus, ovary, prostate pancreas and urinary bladder.

Dose :- 12 mg/kg/day I.V for 4 days followed by 6 mg/kg on alternate days. It is also available as 250 mg capsule form.

2. **cytarabin** used in leukaesmisas in children and adults.

Dose :- 1.5 – 3 mg/kg, I.V, B.D, for 5-10days

3. **Azarabin** is useful in acute leukaesmisas.

Adverse effect:- nausea, vomiting, leucopenia, anaemia, thrombocytopenia, intestinal ulceration.

Purine analogs: - these agent inhibit purine synthesis. Purines adenine and guanine are the constituents of DNA. Hence these agents prevent the formation of DNA. Pentostatin is useful in hairy cell carcinoma, fungoid.

1. **6- Mercacaptopurine (6MP) and 6- Thioguanine (6TG)**:- these are the purine antagonists highly effective for acute leukaemia, choriocarcinoma and solid tumours.

Dose:- 2.5 mg/kg/day

2. **Azathioprine**:- it is purine antagonist . it is derivative of mercptopurine. It is useful immunosuppressive agent: useful in acute and chronic leukaemia.

It is also used as an immunosuppressant in organ transplantation and rheumatoid arthritis.
Dose:- 3-5 mg/kg/day

Adverse effect:- bone marrow depression

Vinca alkalodis :- these agents bind specifically to protein tubulin which is help in formation of microtubules. These agents disrupted the microtubules and blockade of mitotic division of metaphase (spindle is not formed during the cell division)

uses:- in lymphosarcoma, human choriocarcinoma, hodgkin's disease, lymphatic leukaemia, non-Hodgkin lymphoma, cancer of breast, kidney and testes

1. **vincristine (Oncovin)**:- it is rapidly acting drug

dose;- 1.5 mg/m^2 I.V weekly
uses:- leukaemia in children, lymphosarcoma, Hodgkin disease, wilm tumor and lung carcinoma.

2. **Vinblastine** :- used in Hodgkin disease and testicular carcinoma, it cause bone marrow depression and neurotoxicity.

3. **Paclitaxel (taxol):-** it act by interfering with mitosis. It is useful in solid tumours.

Dose:- 175 mg/m^2 I.V / every 3 weeks

Antibiotics :-
these antibiotics interfere with DNA/RNA synthesis. They depress bone marrow, GI upset, alopecia, cardio myopathy, pulmonary fibrosis

1. **Actinomycin-D or Dactinomycin**: - it is red coloured, potent anticancer. It is an antibiotic which bind with DNA and form complex with it and inhibit the synthesis of DNA and RNA.

Dose:- 15 µg/kg I.V daily for 5 days.

Uses:- choriocarcinoma, lymphomas and Hodgkin disease

Adverse effect:- anorexia, nausea, vomiting, bone marrow depression

2. **Daunorubicin and doxorubicin**: - these anticancer antibiotic bind with DNA and disrupts DNA activities. These are highly toxic to myocardium and produce arrhythmias. It also produce bone-marrow depression and hypotension.

Use:- acute leukaemia, lymphomas and adrenosarcoma of breast, bladder and thyroid gland

3. **Mithramycin**: - it interferes with RNA synthesis. It is specifically useful in carcinoma of testes. It is highly toxic and produce myelosuppression, haemorrhage and damage to liver and kidneys.

4. **Mitomycin:**- it produces polymerization of DNA and thereby damage DNA. It is used in cancer of stomach, cervix, colon, breast, pancreas and urinary bladder.

Dose :- 2-10 mg/m^2 daily I.V for 5 days.

5. **Bleomycin**:- this antibiotic interacting with Fe and O_2 in DNA molecules. It should be given prior to radiation therapy.

Dose;- 30 mg I.V or I.M twice weekly.
Uses :- it is specifically useful for squamous cell carcinoma e.g carcinoma of skin, upper respiratory passages, oral cavity and urinogenital tract.
Adverse effect:- nausea, vomiting, hyperpyrexia, headache, hypotension

6. **Daunorubicin**:- 30-60 mg/m2 I.V daily for 3 days

7. **Doxorubicin** :- 60-75 mg/m2 I.V every 3 weeks,
8. **Mitoxantrone** :- 12 mg/m2 IV at 3 weeks intervals.

L- Asparginase:-
it is an enzyme that catalyzes hydrolysis of aspargine to aspartic acid and ammonia. Certain malignant cells require aspargin for their growth. Thus, by metabolizing aspargine, cells are deprived of the compound and growth is inhibited. Asparginase prevent the synthesis of various proteins and produces immunosuppression.

Dose:- 50-200 IU/kg daily for 2-4 week given by I.V OR I.M

Adverse effect:- toxic to liver, kidney and pancreas. It also affect CNS and clotting mechanisms.

Hormones: -

These substance donot kill the malignant cells but slow down their growth. Thus, they are used in combination therapy.

1. **Estrogen** :- these female sex-hormones inhibit cell growth and differentiation. They also block the effects of androgen and cause regressive change in breast in post menopausal women and in prostate gland in males. Thus, they are useful in breast cancer and prostate cancer.

In prostate cancer, the best result are obtained when they are combined with orchidectomy (removal of testes).

Adverse effect:- importence and gyneomastia.

2. **Progestins**:- useful in endometrial carcinomas and breast cancer

3. **Androgens**;- these hormones inhibit the growth of mammary glands. The best result are obtain when combine with oophorectomy (removal of ovaries).

4. **Antiestrogen** (clomiphene, nafoxidine, tamoxifen):- these substance bind with estrogen receptor to cause depletion of cytoplasm . they are useful in breast cancer.

Adverse effect:- nausea, vomiting, vaginal bleeding

Corticosteroids :-

these agent supress the mitosis of lymph gland and hence they are useful in acute lymphatic leukaemias. They provide symptomatic relief from haemorrhage which is associate with malignant lymphomas and myeloid leukaemia. It is also used with cytotoxic agent to give symptomatic relief and assurance of well being.

Interferon alpha:- it is used in hairy cell leukemia, sarcoma, melanoma, renal cell carcinoma

Radio active substance:-

1. **Radium**:- it is bivalent metal. It disintegrates with emission of various types of radiations. Hence, it has been referred to as radioactive. They act on protein molecules and modify their chemical structure. These rays may cause structural change in the chromosomes and chemical change in the genes.

2. **Radioactive Phosphorous (P^{32})**:- it is used in the form of disodium hydrogen phosphate. It is distributed to all parts of the body. It is used in disease lymphatic leukaemia.

3. **Radioactive iodine (I^{131})** :- it is obtained as a fission product of uranium. It is used orally as well as intravenously. It act by giving β- radiation.

Cisplatin :- it enter the cell by diffusion and disrupts the function of DNA. It is useful in testicular and ovarian cancer. It acts by cross linkage of DNA.

Dose:- 100 mg/m^2, every 4 week by IV

Adverse effect:- nausea, vomiting, anaphylaxis, ototoxicity, renal damage, leukopenia, thrombocytopenia, peripheral neuropathy.

Hydroxylurea:- it inhibit ribonucleoside diphosphate reductase that conversion of RNA to DNA.

Use:- chronic grannlocytic leukaemia, malignanat melanoma.

Adverse effect:- git disturbance

Procarbazine ;- it inhibit RNA and DNA synthesis.

Use:- in hodgkin's disease, brain tumor, myeloma

Adverse effect:- nausea, vomiting, leukopenia, thrombocytopenia, CNS depression.

Mitotane :- it inhibit adrenocorticosteriods and decrease corticosteroids level.

Use:- adrenocortical carcinoma

Adverse effect:- nausea, vomiting, lethargy and dermatitis.

Cancer Vaccine:- liver cancer can be prevented by immunization against hepatitis by viral infection.