Chapter 14

MALIGNANT DISEASES AND IMMUNOSUPPRESSION

14: DRUGS USED IN MALIGNANT DISEASES AND FOR IMMUNOSUPPRESSION

Though current treatment is given with curative or palliative intention, the main approaches with dealing malignancies are surgical intervention, radiation and chemotherapy. Treating cancer with cytotoxic drugs is the main method of treatment for only a few malignant disease; but it's increasingly use as an adjunct to surgery or irradiation in a range of common types of malignancy.
In this chapter, drug treatment in malignant diseases and for immunosuppression is discussed under the following headings:

14.1 CYTOTOXIC DRUGS

Like the disease, the treatment of cancer is also a complex one. It is better to take advice from the specialist oncologist. Along with its anti-cancer activity cytotoxic drugs have also the potential for damage to normal tissue. This property determined that drugs could be given intermittently and that time had to be allowed for normal tissues to recover between each administration of cytotoxic drugs. The tumors also rapidly developed resistance to single agents and this is why the intermittent combination chemotherapy principle was

established. Several drugs were combined together, chosen on the basis of differing mechanisms of actions and non-overlapping toxicities. In an increasing number of cases chemotherapy may be combined with radiotherapy or surgery or both as either neoadjuvant (Pre-surgery chemotherapy for early and locally advanced cancer) treatment or as adjuvant (Chemotherapy following local treatment for early cancer) treatment. Drug combination are frequently more toxic than single drug but may have the advantage in certain tumors of enhanced response, reduced development of drug resistance and increased survival. However, for some tumors, single-agent chemotherapy remains the treatment of choice. Cytotoxic drugs may be given with a curative intent or to palliate the symptoms or it may aim to prolong the survival.

Cytotoxic drugs are categorized into different classes according to characteristic anti-tumor activity, sites of action and toxicity.

SIDE EFFECTS OF CYTOTOXIC DRUGS

The side effects of anti-cancer drugs are legendary and have created fear in both the medical profession and the general public. The situation has improved from the early days of cytotoxic chemotherapy where persistent and prolonged nausea and vomiting were the rule and life threatening complications from myelosuppression. Modern cytotoxic chemotherapy has improved out of all recognition from those early days and newer cytotoxic drugs, often analogues of original drugs, are frequently associated with significantly fewer side effects.

Most currently used anticancer drugs have their main effects on cell division; because of this effect they will affect all rapidly dividing normal tissues and thus they are likely to produce, to a greater or lesser extent of the following toxic effects are :

Bone marrow toxicity with decreased leucocyte production and thus decreased resistance to infection, impaired wound healing, depression of growth in children, sterility, teratogenecity, loss of hair, and damage to gastrointestinal epithelium.

They can also in certain circumstances, be carcinogenic. A number of cytotoxic drugs will cause severe local tissue necrosis if leakage into the extravascular compartment occurs. In addition, if there is rapid cell destruction with extensive purine catabolism, urates may precipitate in the renal tubules and cause kidney damage. All cytotoxic drugs produce severe nausea and vomiting. Some compounds have particular toxic effects which are specific for them. These will be discussed under the individual drugs.

WARNINGS

Cytotoxic drugs should be administered under the supervision of a physician with sufficient experience in cancer chemotherapy at medical institutions in which appropriate medical treatment can be made in emergency to the patients.

REGARDING DOSAGE REGIMENS

Although dose statements have been given in this chapter, still product literature needs to be consulted.

Despite the advances, chemotherapy still carries many potentially serious side effects and should be used only by practitioners with considerable skills and experiences. The main side effects with anticancer drugs such as bone marrow suppression, emesis, extravasation, hyperuricaemia are described below with the measures to control them.

Nausea and vomiting: is the most common terrified effect of cancer treatment. The incidence and severity of nausea and vomiting varies depending on the type, dose, schedule, combination of medication of chemotherapy and the patient's characteristics. Symptoms may be acute (occurring with in 24 hours of treatment), delayed (occurring after 24 hours of initiating treatment) and anticipatory (occurring prior to subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute one and require different managements.

Severe vomiting can be produced by the platinum based drugs such as dacarbazine, high doses of cyclophosphamide, cisplatin and taxene. Moderately emetogenics are doxorubicine, intermediate and low dose of cyclophoshamide, mitoxantrone and high dose of methotrexate (0.1 – 1.2 g/m^2). The less severe or mild emesis is found with fluorouracil, etoposide, methotraxate (less than 100 mg/m^2), the vinca alkaloids and abdominal radiotherapies.

To prevent emesis a specific ($5HT_3$) serotonin antagonist, **granisetron** is used. The $5HT_3$ antagonists are highly effective in controlling early emesis and have largely replaced the use of high-dose of intravenous **metoclopramide**. Granisetron can more readily be given as a single intravenous dose for patients receiving cisplatin and non-cisplatin based regimes. In addition it is approved for oral use for cisplatin-based (highly emetogenic) antineoplastic therapy unlike ondansetron. The 5HT3 receptor antagonists [Granisetron] currently marketed have proved to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Further there is no good scientific rationale for the use of 5HT3 antagonists in treating delayed nausea and vomiting since serotonin has not been shown to be released during the delayed phase. The addition of **lorazepam** to antiemetic therapy is sometimes helpful to prevent anticipatory symptoms.

Extravasation: or leakage of cytotoxic drugs into the extravascular compartments leads several local tissue necrosis. To reduce the risk of extravasation injury it is recommended that they should be given by appropriately trained hands. Attention should be paid to the manufactures' recommendations for administration. Patients should be asked to report any pain or burning at the site of injection immediately.

Hyperuricaemia: which can result in uric acid crystals formation in the urinary tract with associated renal dysfunction is a major complication of treatment of non-Hodgkin's lymphoma, leukaemia and myelo-proliferative diseases. Patients should be adequately hydrated. Increased urinary volume decreases the concentration of urate in urine and thus minimizes the problem. Alkalinisation of urine should be initiated to maintain urine pH at least 7. Other than this, Allopurinol should be started 24 hours before treating such tumors, and should be continued for 7-10 days; The dose of Mercaptopurine or Azathioprine should be reduced if Allopurinol needs to be given concomitantly.

Bone Marrow Suppression: is caused by all the cytotoxic drugs except vincristine and bleomycine. It commonly occurs 7-10 days after administration, but also delayed in certain drugs, such as carmastine, lomustine, and melphalan. To overcome these problem peripheral blood counts must be checked before each treatment, and doses should be reduced or therapy delayed if bone marrow has not recovered.

Fever in a neutropenic patient should receive parental broad-spectrum antibiotics. Appropriate culture and sensitivity tests should be done as soon as possible.

Colony stimulating factors, G-CSF are sometimes successful in selected

patients depending on the duration and severity of the neutropenia.

Alopecia: many but not all the cytotoxic drugs are capable of causing hair loss. Scalp cooling can sometimes be used to reduce hair loss with doxorubicine, but in general this side effect can be prevented only by selection of cytotoxic drugs where this is possible. Hair always regrows on completion of chemotherapy. No pharmacological methods of preventing reversible hair loss are available.

Pregnancy: most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during first trimester.

Cardio-toxicity: this is a rare side effect of chemotherapy, usually associated with doxorubicine. It is dose related and can largely be prevented by keeping the total dose with in the safe range.

Neuro-toxicity: this occurs predominantly with the plant alkaloids and platinum analogues. It is dose related and chemo therapy usually stopped before the development of the significant polyneuropathy. This is only partially reversible.

Sterility: some anticancer drugs, specially alkylating agents, may cause sterility. This can be irreversible. In male storage of sperm is the only important consideration when chemotherapy is given with curative intentions.

Drugs to prevent cytotoxic-induced side-effects

Methotrexate-induced mucosities and myelosuppression

Folinic acid (calcium folinate) is used to counteract the folate-antagonist action of methotrexate and thus speed recovery from methotrexate-induced mucositis and myelosuppression.
When folinic acid and fluorouracil are used together in metastatic colorectal cancer the response-rate improves compared to that with fluorouracil alone *(see also section 15.1.2.1).*

Levofolinic acid: The calcium salt of levofolinic acid is the single isomer of folinic acid. It is used as folinic acid. The dose of levofolinic acid is half of folinic acid.

CALCIUM FOLINATE

(Calcium leucovorin)

Indications: methotrexate induced mucositis and myelosuppression

Cautions: avoid simultaneous administration of methotrexate, not indicated for pernicious anemia or other megaloblastioc anemia due to vitamin B12 deficiency; pregnancy and breast-feeding

Interactions: antiepileptics; plasma concentration of phenobarbital, phenytoin and primidone possibly reduced *(see also Appendix-2)*

Contraindication: intrathecal injection.

Side-effects: rarely pyrexia after parental use

Dose: expressed in terms of folinic acid

As an antidote to methotrexate (usually started 24 hours after the beginning of methotrexate infusion), usually up to 120 mg in divided doses over 12-24 hours by intramuscular *or* intravenous injection or intravenous infusion, followed by 12-15 mg intramuscularly or 15 mg by mouth every 6 hours for the next 48 –72 hours.

Suspected methotrexate overdose, immediate administration of folinic acid at a rate not exceeding 160 mg/minute in a dose equal to (or higher than) the dose of methotrexate

Proprietary Preparations
Biofol *(Incepta),* Tab. 15 mg, Tk. 25.00/Tab.
Folinex *(Beacon),* Inj. 50mg/ml, Tk.500.00/Vial

CALCIUM LEVOFOLINATE

(Calcium levoleucovorine)

Indications: same as that of calcium folinate

Cautions: same as that of calcium calcium folinate

Side-effects: same as calcium folinate

Dose: express in terms of levofolinic acid

As an antidote to methotrexate (usually started 24 hours after the beginning of methotrexate injection), usually 7.5 mg, by intramuscular injection or by intravenous injection or by intravenous infusion every 6 hours for 10 doses

Suspected methotrexate overdose, immediate administration of levofolinic acid at a rate not exceeding 160 mg/minute in a dose which is a least 50% of the dose of methotrexate

Proprietary Preparation
Leucovorine[I] *(Mayne),* Inj. 50mg/ml Tk.377.09/vial, Tk.15mg/2ml, Tk.228.78/vial

PLATINUM-INDUCED NEUTROPENIC INFECTION AND NEPHROTOXICITY

Granulocyte colony stimulating factor and granulocyte macrophage-colony stimulating factor are used for the reduction of risk of infection associated with neutropenia.

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils and may reduce the duration of chemotherapy induced neutropenia and thereby reduce the incidence of associated sepsis; there is yet no evidence that it improves overall survival. Filgrastim (unglycosylated rhG-CSF) and lenograstim (glycosylated rhG-CSF) have similar effects; both have been used in a variety of clinical settings but they do not have any clear-cut routine indications. Prolonged use may be associated with increased risk of malignancy. Molgramostim (Recombinant human granulocyte macrophage colony stimulating factor) stimulates the production of all granulocytes and monocytes. It has more side-effects than granulocytes colony stimulating factor and is ineffective in congenital neutropenia.

FILGRASTIM

(Recombinant human granulocyte colony stimulating factor, G-CSF) *(see also section 15.1.4)*

Indications: (specialist use only) reduction duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukemia and myelodysplstic syndromes); reduction in duration of neutropenia (and associated sequel) in myeloablative therapy followed by bone marrow transplantation; mobilization of peripheral blood progenitor cells for harvesting and subsequent autologous infusion; severe congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia and history of severe or recurrent infections (distinguish carefully from other haematological disorders, consult product literature); persistent neutropenia in advanced HIV infection

Cautions: reduced myeloid precursors; monitor leucocyte count (discontinue treatment if leucocytosis, consult product literature); monitor platelet count and haemoglobin; regular morphological and cytogenetic bone marrow examinations recomended in severe congenital neutropenia (possible risk of myelodysplastic syndromes or leukaemia); monitor the spleen size, osteoporotic bone disease (monitor bone density if given for more than 6 months); does not prevent other toxic effects of high dose chemotherapy; pregnancy, breast feeding

Interactions: possible exacerbation of neutropenia with fluorouracil

Note: use not recommended in period from 24 hours before to 24 hours after chemotherapy - for further details consult product literature.

Contraindications: severe congenital neutropenia with abnormal cytogenetics

Side-effects: musculoskeletal pain, transient hypotension, disturbances in liver enzymes and serum uric acid; thrombocytopenia; urinary abnormalities including dysuria; allergic reactions

(more common after intravenous infusion), proteinuria, haematuria, and transient decrease in blood glucose reported; cutaneous vasculitis also reported, also spleenic enlargement, hepatomegaly, headache, diarrhoea, anaemia, epistaxis, alopecia, osteoporosis and rash, reactions at injection site; rarely reported, exacerbation of rheumatoid arthritis, adult respiratory distress syndrome

Dose: cytotoxic-induced neutropenia, preferably by subcutaneous injection or by intravenous infusion (over 30 minutes), ADULT and CHILD, 50,00,000 units/kg daily started not less than 24 hours after cytotoxic chemotherapy, continued until neutrophil count in normal range, usually for up to 14 days (up to 38 days in acute myeloid leukaemia)

Proprietary Preparations

Filastin *(Incepta),* Inj.,(P.F syringe) 300 mcg/0.5 ml, Tk. 2,890.00/Syringe
Filgrast *(Beacon),* Inj., (P.F syringe) 300 mcg/0.5 ml, Tk. 2,750.00/ Syringe
Grastim *(Square),* Inj.,(P.F syringe) 300 mcg/0.5 ml, Tk. 3,950.00/Syringe
Neufil *(Healthcare),* Inj.,(P.F syringe) 300 mcg/0.5 ml, Tk.3,920.00/ Syringe
Neupogen (I) *(Roche),* Inj., 30 MIU, Tk. 8,000.00/Vial
Zarzio(I) *(Sandoz),* Inj.,(P.F syringe) 30 MIU/0.5 ml, Tk. 21,000.00/0.5 ml Syringe

LENOGRASTIM

(Recombinant human granulocytecolony stimulating factor, rhG-CSF)

Indications: (specialist use only) reduction in the duration of neutropenia and associated complications following bone marrow transplantation for nonmyeloid malignancy or following treatment with cytotoxic chemotherapy associated with significant incidence of febrile neutropenia; mobilisation of peripheral blood progenitor cells for harvesting and subsequent infusion

Cautions: *see under filgrastim;* premalignant myeloid conditions

Interactions: use not recommended from 24 hours before until 24 hours after chemotherapy. *For further details consult product literature*

Dose: cytotoxic induced neutropenia, by subcutaneous injection, ADULT 19.2 million units/sq.m. daily started the day after completion of chemotherapy, continued until neutrophil count is stable in acceptable range (max. 28 days)

Proprietary Preparation

Granocyte(I) *(Sanofi Winthrop),* Inj. 34 MIU/ vial, Tk. 5961.54/Vial

Amifostine is used recently for the reduction of risk of infection related to neutropenia in patients undergoing treatment with cisplatin and cyclophosphamide and for the reduction of nephrotoxicity due to cisplatin. It is also used recently to protect against xerostomia during radiotherapy for head and neck cancer.

UROTHELIAL TOXICITY

Haemorrhagic cystitis is a common manifestation of urithelial toxicity which occurs with the oxazaphosphorines, cyclophosphamide and ifosfamide; it is caused by the metabolite acrolin. Mesna reacts specifically with this metabolite in the urinary tract, preventing toxicity. Mesna is used routinely (preferably by mouth) in patients receiving ifosfamide, cyclophosphamide by intravenous route at a high dose (more than 2 g) or in those who experienced urothelial toxicity when given cyclophosphamide previously.

MESNA

Indications: *see notes above.*

Contraindications: hypersensitivity to thiol containing compounds

Side-effects: nausea, vomiting, colic, diarrhea, fatigue, headache, limb and joint pains, depression, irritability, rash, hypotension and tachycardia

Dose: calculated according to oxalophosphorine (cyclophosphamide or ifosfamide) treatment. When given by

mouth, dose is given 2 hours before oxalophosphorine treatment and repeated 2 and 6 hours after treatment; when given by intravenous injection, dose is given with oxalophosphorine treatment and repeated 4 and 8 hours after treatment

Proprietary Preparations

Ifomes *(Beacon),* In.j, 400 mg/Vial, Tk. 190.00/Vial
Mesna *(Techno),* Inj., 400 mg/Vial , Tk. 240.00/Vial
Uromitexan [I] *(Baxter),* Inj. 400 mg/4 ml, Tk. 4474.50/4 ml Vial

14.1.1 ALKYLATING DRUGS

The anti-tumor alkylating agents are the oldest class of anti-cancer drugs. These molecule represents the first examples of the application of scientific rigor to the clinical development of drugs for the treatment of cancer and the first example where a knowledge of the properties of the cancer cells was applied to rational drug design. The anti-tumor alkylating agents are the most widely used anti-cancer drugs, being major components of the combination chemotherapy regimens for the disseminated solid tumors and for high dose/stem cell support treatment regimens. The agents having alkyl group can form covalent bonds with the cellular DNA, resulting inhibition or inaccurate cell replication with resultant mutation and cell death. Cyclophosphamide is a broadly active anti-cancer drug. It has pronounced effect on lymphocytes and is used as an immunosuppressant. It is used in combination chemotherapy regimens for non-Hodgkin's lymphoma, leukaemia, Hodgkin's disease, Burkit's lymphoma, breast cancer, ovarian carcinoma, endometrial carcinoma, small cell lung carcinoma, multiple myeloma, sarcomas. Cyclophosphamide is also a useful agent in high dose regimen for lymphoma and solid tumors. It is usually given orally or by intravenous injection but may also be given intramuscularly or into the pleural or peritoneal cavities. Important toxic effects are nausea, vomiting, myelosuppression, sterility, risk of acute non-lymphocytic leukaemia and haemorrhagic cystitis. Cyclophospha-mide is a prodrug that is activated to give aldophosphamide, which is then converted to phosphoramide mustard, the cytotoxic molecule and acrolin which causes haemorrhagic cystitis that can be ameliorated by Mesna and by increasing fluid intake.

Busulfan (busalphan) has a selective effect on bone marrow, depressing the formation of granulocytes and platelets in low dosage and red cells in higher dosage. It has little or no effect on lymphoid tissue or the gastrointestinal tract. It is accordingly used in chronic granulocytic leukaemia, in which it may increase the life expectancy by about a year. It has a hazardous toxic effect, thrombocytopenia. Hyperpigmentation of skin is a common side-effect and rarely progressive pulmonary fibrosis may occur. Frequent blood count is essential to monitor bone marrow aplasia. Busulfan is to be given with cyclophosphamide in a preparatory regimen for bone marrow transplant in the treatment of refractory leukemias, lymphomas and several paediatric solid tumors.

Carmustine is given intravenously. It has similiar activity and toxicity to lomustine. This drug is used for myeloma, lymphoma, brain tumors. Cumulative renal damage and delayed pulmunary fibrosis may occur.

Chlormethine (mustine) is now much less commonly used. It is a very toxic drug which causes severe vomiting. The freshly prepared injection must be given into a fast-running intravenous infusion. Local extravasation causes severe tissue necrosis.

Chlorambucil, the phenylebutyric acid derivative of nitrogen mustard, was synthesized, like Melphalan in an attempt to produce a nitrogen mustard with greater efficacy than mechlorethamine. Chlorambucil is relatively stable in aqueous solution and is well absorbed in oral administrations. This is commonly used in chronic

lymphocytic leukaemia, Hodgkin's and non-Hodgkin's lymphoma, choriocarcinoma, ovarian carcinoma, breast cancer. Chlorambucil is administered either as a single agent or combination with prednisone. Side-effects apart from marrow suppression are uncommon. However, occasionally patients develop severe widespread rashes that can progress to toxic epidermal necrolysis. If rash occurs further chlorambucil is contraindicated and cyclophosphamide is substituted.

Estramustine is a combination of mustine with an estrogen used predominantly in prostate cancer. It is given by mouth and has both antimitotic effect and hormonal effect.

Ifosfamide originated from the same chemical synthesis program that had produced cyclophosphamide. Ifosfamide is a pro-drug like cyclophosphamide, and is highly active in soft tissue sarcoma and produced significant response rate in non-small cell lung cancer. Ifosfamide is administered intravenously. Although it causes less myelosupression than cyclophosphamide, it produces dose-limiting cystitis. Mesna given prior to, during, and after ifosfamide or simultaneously with ifosfamide prevents haemorrhagic cystitis.

Lomustine may act on non-dividing cells and can cross blood brain barrier (BBB); it is mainly used in the treatment of primary and metastatic brain tumor, and advanced Hodgkin's disease. This cytotoxic agent causes delayed, cumulative myelotoxicity and the drug is therefore given at intervals of 4 to 6 weeks. Permanent bone marrow damage may occur with prolonged use. Nausea and vomiting are common and moderately severe.

Melphalan is used in the treatment of myeloma, occasionally solid tumor and lymphomas. It is given by mouth. Because bone marrow toxicity is delayed the drug is usually given at intervals of 4-6 weeks.

Mitobronital is sometimes used to treat chronic myeloid leukemia.

Treosulfan is given by mouth or intravenously and used to treat ovarian cancer. Skin pigmentation is the common side-effect and allergic alveolitis, pulmonary fibrosis and haemorrhagic cystitis occur rarely.

Thiotepa is used as an intracavitary drug for the treatment of malignant effusions or bladder cancer. It is also occasionally used to treat breast cancer, but require parental administration.

BUSULFAN

(Busulphan)

Indication: chronic myeloid leukemia.

Caution: *see section 14.1*

Side-effects : *see section 14.1and notes above*

Dose : ADULT: induction of remission, 60 micrograms/kg to max 4 mg/m^2 daily until the leucocyte count is 50% of the original level; maintenance, 0.5-2 mg/m^2 daily. CHILD: not recommended

Generic Preparation

Tablet. 2 mg.

CHLORAMBUCIL[ED]

Indications: chronic lymphocytic leukemia, low grade non-Hodgkin's lymphoma; ovarian carcinoma.

Caution: *see section 14.1 and avoid in porphyria*

Side-effects: *see section 14.1and notes above*

Dose: used alone, usually 100-200 micrograms/kg daily for 4-8 weeks

Proprietary Preparation

Leukeran (I) *(GSK*), Tab. 2 mg

CYCLOPHOSPHAMIDE [ED]

Indications: breast, lung, ovary, testis and bladder carcinomas. Bone and soft tissue sarcomas
Hodgkin's and Non-Hodgkin's lymphomas. acute and chronic lymphocytic leukaemias, neuroblastoma

and Wilm's tumor of childhood, multiple myeloma.

Cautions: hepatic and renal impairment

Interactions: anticoagulants, pentostatin (avoid concomitant use), muscle relaxants (enhance the effect of suxamethonium) *(see also Appendix-2)*

Side-effects: *see section 14.1*

Dose: high dose therapy: 20-40mg/kg as a single I.V. dose given at 10-20 days intervals. Medium dose therapy: 10-15 mg/kg as a single I.V. dose weekly. Low dose therapy*:* 2-6 mg/kg as a single I.V. dose or in divided oral dose for 7 days & maintenance 100-200 mg daily. CHILD not recommended

Proprietary Preparations
Cyclomide *(Techno),* Inj, 1 gm Vial, Tk.1,200.00/Vial
Cyclotox *(Beacon),* Inj., 1 gm Vial,Tk.650/Vial; Inj., 200mg Vial, Tk.180.00/Vial
Endoxan[(I)] *(Baxter),* Inj., 200mg, Tk. 3114.2/Vial; 500mg, Tk. 20.52/Vial; 1gm, Tk. 1374.56/Vial; Tab., 50mg, Tk. 1718/Tab.
G-Cyclophosphamide *(Gonoshasthaya),* Tab., 50 mg, Tk. 6/Tab.

IFOSFAMIDE

Indications: tumors of testes, pancreas, ear; nose & throat, ovary, bone, breast, lungs, G I Tract, kidneys; lymphomas and soft tissue sarcomas

Cautions: *see section 14.1;* reduce the dose in hepatic and renal impairment

Interactions: *see Appendix-2*

Side-effects: *see the side-effects of cytotoxic drugs*

Dose: 8-10 g/m^2 IV fractionated equally to single daily dose for 5 consecutive days or a 24 hours infusion of 5-6 g/m^2; use in combination with Mesna (60% of total dose of Ifosfamide)

Proprietary Preparations
Holoxan[(I)] *(Baxter),* Inj., 1g, Tk. 3049.8/1 gm Vial; 2g, Tk. 4810.58/2 gm Vial
Ifamide*(Techno),* Inj., 1 gm/vial, Tk. 2,400.00/Vial ; 2 gm/vial, Tk. 4,500.00/Vial
Xifos *(Beacon),* Inj., 1 gm/vial, Tk. 1,800.00/Vial; 2 gm/vial, Tk. 3,200.00/Vial

LOMUSTINE

Indications: *see note above.*

Cautions: *see section 14.1 and notes above*

Side-effects: *see section 14.1and notes above*

Dose: used alone, 120-130 mg/m^2 PO once every 6-8 weeks

Generic Preparation
Capsule 10mg

MELPHALAN

Indications: mainly multiple melanoma, breast and ovarian cancers

Cautions: *see the side-effects of cytotoxic drugs and renal impairment*

Interactions: nalidixic acid (increased toxicity), cyclosporin (renal impairment);

see also Appendix-2

Side-effects: *see the side-effects of cytotoxic drugs and notes above*

Dose: *by mouth* 150 micrograms/kg daily in divided doses for 4 days repeated at an interval of 6 weeks

Proprietary Preparation
Alkeran *(GSK)*,Tab.,2mg

14.1.2 CYTOTOXIC ANTIBIOTICS

Drugs in this group are used widely. Anthracyclines are mainly termed as cytotoxic antibiotics. The first anthracyclines in clinical use, **doxorubicin** and **daunorubicin**, were produced by *Streptomyeces* species. The second generation **idarubicin**, **epirubicin** are synthetic anthracyclines. **Mitoxantrone** (mitozantrone) is an anthracycline derivative. **Anthracyclines**, DNA intercalators represent the most important class of anticancer drugs.

Doxorubicin is one of the most successful and widely used anti-tumor drugs. It is used to treat the acute leukaemia's, lymphomas and a variety of solid tumors. It acts by DNA strand

breakage mediated by anthracycline effects on topoisomerase II, the activity of which is markedly increased in proliferating cells. It is given by fast running infusions, commonly at 21 days intervals. After infusion it is rapidly taken up by most tissues, but does not cross the Blood Brain Barrier (BBB). Extravasation at the infusion site can cause local necrosis. It is also been given in bladder instillation. Evidence is available to suggest that weekly low dose administration may be associated with less cardiac damage. It is excreted mainly in the bile. In addition to the side effects common to other cytotoxic agents, doxorubicin can cause cumulative dose related cardiac damage, leading to arrhythmias and heart failure. Patients with pre existing cardiac disease, the elderly, and those who have received myocardial irradiation should be treated cautiously. Marked alopecia frequently occurs.

Epirubicin is structurally related to doxorubicin and clinical trials suggest that it is as effective in the treatemnt of breast cancer. A maximum cumulative dose of 0.9-1 g/m^2 is recommended to help to avoid cardiotoxocity. Like doxorubicin it is given intravenously and bladder instillation.

Aclarubicin and **idarubicin** are anthracyclines with general properties similar to those of doxorubicin. They are both given intravenously. Idarubicin may also be given by mouth.

Daunorubicin also has general properties similar to those of doxorubicin. It should be given by intravenous infusion and is indicated for acute leukaemias.

Mitoxantrone (mitozantrone) is structurally related to doxorubicin. It's main use is in breast cancer though it is also licensed to use in non Hodgkin's lymphoma and adult non lymphocytic leukaemia. It is given intravenously and well tolerated but myelosuppression and dose related cardiotoxicity occurs.

Bleomycin is a group of metalchelating glycopeptide antibiotics that degrade preformed DNA, causing chain fragmentation and release of free bases. It is given intravenously or intramuscularly to treat the lymphoma's, and germ cell tumors of testis and ovary and also some other solid tumors. With it's little bone marrow suppression it causes dermatological toxicities and increased pigmentation. Most serious toxic effect is pulmonary fibrosis. Basal lung crepitations or suspicious chest X-ray changes are indications to stop therapy with this drug. Allergic reactions can occur. Many develop hyperpyrexia a few hours after drug administration and may be prevented by simultaneous administration of corticosteroid.

Dactinomycin is one of a series of antibiotics obtained from *Streptomyces* microorganisms, principally used in paediatric cancer. It prevents transcription and has a similar action to the anthracyclines on topoisomerase II. It has effects on cells in all phases of the cell cycle, but it is particularly potent on rapidly proliferating cells. It has all the cytotoxic effects described under side effects of cytotoxic drugs. It is usually given by IV injection and rapidly disappears from the plasma and does not cross the BBB.

Mitomycin is given intravenously to treat upper gastro intestinal and breast cancers and by bladder instillation for superficial bladder tumors. It causes delayed bone marrow toxicity and therefore it is usually administered at 6 weeks intervals. Prolonged use may result in permanent bone marrow damage. It may also cause lung fibrosis and renal damage.

BLEOMYCIN [ED]

Indications: squamous cell carcinoma, lymphomas, germ cell tumors of testis and ovary and certain solid tumors

Cautions: *see section 14.1*; renal impairment; irritant to tissue

Side-effects: *see section 14.1* and *see notes above*

Dose: over 80 years, 15 mg/week, total 100mg; 70-79 years, 30 mg/week, total 150-200 mg; 60-69 years, 30-60 mg/week, total 200-300 mg; under 60 years, 30-60 mg/week, total 500 mg; all are given I.V. or in infusion

Proprietary Preparation
Bleocin [I]*(Nippon),* Inj. 15000unit/vial Tk. 2063.99/vial

DACTINOMYCIN

(Actinomycin D)

Indications: gestational trophoblastic neoplasms, Wilm's tumor, rhabdomyosarcoma and Ewing's sarcoma of childhood

Cautions: *see section 14.1*; caution in handling- irritant to tissue

Side-effects: *see section 14.1 and see notes above*

Dose: CHILD: 0.40-0.45 mg/m^2 (up to maximum of 0.5 mg) IV daily for 5 days every 3-5 weeks.

ADULT: 0.40-0.45 mg/m^2 IV on days. 1-5 every 2-3 weeks. 0.5 mg IV daily for 5 days every 3-5 weeks.

Generic Preparation
Injection. 100 microgram/vial.

DAUNORUBICIN HYDROCHLORIDE

Indications : *see notes above.*

Cautions: hepatic and renal impairment; caution in handling-irritant to tissue (*see section 14.1*)

Side-effects : *see section 14.1* and *see notes above*

Dose : 30 to 45 mg/m^2 IV for 3 days; using extravasation precautions; to be injected into a recently established patent IV site through side arm of a running IV over 2 to 5 minutes; courses may be repeated after 3 to 6 weeks.

Proprietary Preparation
Rubicin *(Beacon)*, Inj., 20mg/vial, Tk. 600/Vial

DOXORUBICIN HCL [ED]

Indications: lymphoma, leukemia, breast cancer, ovarian cancer, sarcomas and varieties of solid tumors

Cautions: hepatic and renal impairment caution in handling - irritant to tissue (*see section 14.1)*

Interactions: *see Appendix-2.*

Side-effects: *see section 14.1*and *see notes above*

Dose: 60-75 mg/m^2 I.V. every 3 weeks. 30 mg/m^2 I.V. one days 1 and 8 every 4 weeks (in combination). 15-20 mg/m^2 instilled into bladder weekly for 4 weeks

Proprietary Preparations
Doxorubicin HEXAL[I] *(Hexel),* Inj., 10 mg/5 ml, Tk. 307.00/5 ml Vial; 100 mg/50 ml, Tk. 1,725.00/50 ml Vial; 200 mg/100 ml, Tk. 3,080.00/100 ml Vial; 50 mg/25 ml, Tk. 1,096.00/25 ml Vial
Doxorub *(Techno),* Inj., 10 mg/Vial, Tk. 406.00/10 ml vial ; 50 mg/Vial, Tk. 1,590.00/50 ml vial
Sindroxocin[I] *(Actavis),* Inj., 50mg/vial, Tk. 1560.00/vial; Inj., 10 mg/Vial, Tk.670.00/vial
Xorubion *(Beacon),* Inj., 10 mg/Vial, Tk. 300.00/10 ml/vial; 50 mg/Vial, Tk. 1,000.00/50 ml Vial

EPIRUBICIN HYDROCHLORIDE

Indications: *see notes above*

Cautions: hepatic impairment; caution in handling - irritant to tissue (*see section 14.1)*

Side-effects: *see section 14.1 and notes above*

Dose: 70 to 90 mg/m^2 as a bolus injection repeated every 3 to 4 weeks; bolus injection over 2 to 5 minutes or as a continuous infusion through a central venous catheter

Proprietary Preparations
Erubin *(Beacon),* Inj., 10 mg/ 5 ml , Tk. 915.00/5 ml ; 50 mg/25 ml, Tk. 3,700.00/25 ml
Episindan[I] *(Sindan),* Inj. 2 mg/ml, Tk. 3,866.00/25 ml;Tk.971.00/5ml vial
Pharmorubicin[I] *(Pharmacia),* Inj. 50 mg/Vial, Tk. 3704.60/Vial

MITOMYCIN

Indications: *see notes above*

Cautions: hepatic impairment; caution in handling - irritant to tissue; *(see section 14.1)*

Side-effects: *see section 14.1and notes above*

Dose: 20 mg/m^2 I.V. on day every 4-6 weeks. 2 mg/m^2 I.V. on days 1-5 and 8-12 every 4-6 weeks. 30-40 mg instilled into bladder weekly for 4-8 weeks then monthly for 6 months

Proprietary Preparations
Mitomycin-C Kyowa (I) *(Kyowa)* Inj. 10mg/vial, Tk.729.20/vial, Inj. 2mg/2ml, Tk.193.28/vial

14.1.3 ANTIMETABOLITES

Antimetabolites are the chemotherapeutic agents that includes folate antagonists, purine and pyrimedine analogue.

Methotrexate (antifolate) inhibits a key enzyme in the thymidylate cycle, dihydrofolate reductase (DHFR) essential for DNA synthesis. Methotrexate is taken up into cells by the folate carrier, and like folate, converted to the polyglutamate form. It is given orally, intravenously, intramuscularly or intrathecally. Methotrexate is used in childhood leukemia, non-Hodgkin's lymphoma, gestational trophoblastic tumors, breast cancer, urinary bladder cancer, head neck cancer, lung cancer, gastrointestinal cancer and osteogenic sarcoma. Intrathecal methotrxate is used in prophylaxis of childhood acute leukemia and a therapy for established meningeal cancer or lymphoma. Methotrexate causes myelosuppression and possible nephrotoxicity due to precipitation of the drug or metabolite in the renal tubule. It is contraindicated in significant renal impairment because primarily the kidney excretes it. It may cause damage to the gastrointestinal epithelium. It should be avoided in severe hepatic impairment; should not be given in pleural effusion or ascites because it tends to accumulate at these sites, and its subsequent return to the circulation will be associated with myelosuppression. Systemic toxicity may occur following intrathaecal administration and blood counts should be monitored carefully. High dose regimes (doses 10 times greater than the standard doses) must be followed by "rescue" with folinic acid.

Cytosine Arabinoside (cytarabin) inhibit the synthesis of pyrimidine. It is given subcutaneously, intravenously or intrathecally. It is able to cross BBB with moderate efficiency. The main side effects are on the bone marrow and gastrointestinal epithelium. It is one of the important drugs in the treatment of acute myeloid leukemia and, to a lesser extent, is used in chronic myelogenous leukemia and non-Hodgkin's lymphoma. Using high dose cytarabin regimen, additional toxic effects such as intrahepatic cholestasis and central nervous system toxicity are frequently observed.

Fludarabine is a fluorinated nucleotide analogue of the antiviral vidarabine *(see section 1.4)* which acts as a purine antagonist antimetabolite.It is used for its antineoblastic properties in the treatment of chronic lymphocytic leukaemia (CLL) after initial treatment with alkylating agent has failed. Fludarabine phosphate is given by bolus injection or by IV infusion over 30 minutes in a usual dose of 25 mg/m^2 body-surface daily for 5 consecutive days. Courses may be repeated every 28 days. Fludarabine is generally well tolerated. Bone marrow suppression from fludarabine is dose-limiting, manifesting as leucopenia, thrombocytopenia and anemia. Myelosuppression can be severe and cumulative. CNS and pulmunary toxicity, visual disturbances, heart failure, and autoimmune haemolytic anemia have been reported rarely. Haematological function should be monitored regularly; the dosage may need to be reduced, or further courses delayed, if blood counts indicate severe or persistent myelosuppression.

Cadribine is an effective but potentially toxic drug given intravenous infusion for the treatment of hairy cell leukemia. It is also given in chronic lymphocytic leukemia (CLL) in patients who have failed to respond to standard regimens containing an alkylating agent. Myelosuppression may be severe and serious neurotoxicity has been reported.

Gemcitabine is an analogue of cytrabine, which is metabolised intracellularly to active diphosphate and triphosphate nucleosides, which inhibit DNA synthesis. It is given in the management of solid tumours including those of lungs and pancreas. It is given intravenously. Myelotoxicity reported to be modest even at the high dose of Gemcitabine. Pulmonary oedema, alopecia, influenza-like symptoms, gastrointestinal side-effects, rashes and hypotension have also been reported.

Severe toxicity, in the form of life-threatening oesophagitis and pneumonitis has been seen in patients given radical radiotherapy. Gemcitabine should not be used concurrently with radiation therapy. Gemcitabine should be used with caution in renal and hepatic impairment. Haemolytic uraemic syndrome has been reported rarely and gemcitabine should be discontinued if signs of microangiopathic haemolytic anemia occur.

Fluorouracil (FU), a pyrimidine analogue, is an antineoplastic that acts as an antimetabolite to uracil.It interferes with the synthesis of DNA; it can also interfere with RNA synthesis. It also has immunosuppressant properties.

FU is used alone or in combination in the adjuvant treatment of breast and gastrointestinal cancer, and palliation of inoperable malignant neoplasm, especially those of gastrointestinal tract, breast, head and neck, genitourinary system and pancreas. FU is sometimes used with folinic acid in colonic cancer as adjuvant therapy and as first line therapy in advanced and metastatic colonic cancer.

FU is given usually intravenously because absorption following oral administration is unpredictable. The toxic effects of FU may be severe and sometimes fatal which include bone marrow suppression, gastrointestinal ulceration, bleeding, severe diarrhoea or haemorrhage from any site, leucopenia, thrombocytopenia, stomatitis and rarely cerebellar disturbances. The cytotoxic effect of fluorouracil enhances with other cytotoxic drugs such as cisplatin, methotrexate and with radiation *(see also Appendix-2)*.

Capecitabine: which is metabolized to fluorouracil, is given by mouth as monotherapy in metastatic colorectal cancer it has been shown to be of similar efficacy as a combination of fluorouracil and folinic acid. Oral fluorinated pyrimidine (a prodrug of 5FU) that depends upon carboxyl esterase and thymidine phosphorylase enzymees for activation, is of interest because it may be preferentially activated in tumors compared with normal tissues. Preferential activation at the tumor cell may increase the therapeutic index by producing higher cytotoxicity in colon cancer cells compared with non-neoplastic cells. It is given in colorectal cancer, breast cancer, and other gastrointestinal tract malignancy. Some patients complain with a mild redness of the palm of the hand or sole of the foot which is known as “Hand foot syndrome” is easily reversible. Other than this no other side effects are observed.

Raltitrexed a thymidylate synthase inhibitor, is given intravenous infusion. It is the front line treatment of advanced colorectal cancer when FU and folinic acid cannot be used. It is probably of similar efficacy to FU. **Raltitrexed** is generally well tolerated, but can cause marked myelosuppression and gastro-intestinal side-effects.

Mercaptopurine is a purine analogue, produces cytotoxic actions by many different mechanisms and has several inhibitory actions on de novo purine synthesis and they may themselves be incorporated into DNA. It is well

absorbed when given orally. It is generally administered orally.

It is inactivated by Xanthine Oxidase (XO). XO inhibitor, allopurinol (a purine analogue) inhibits the breakdown of mercaptopurine and increases both its effect and toxicity. Other purine analogue, azathioprine, which gives rise to mercaptopurine *in vivo*, is used for non-malignant conditions such as immunosuppression *(see section 14.2.2)*. The dose of both drugs should be reduced if the patient is receiving allopurinol since it interferes with their metabolism. **Mercaptopurine** is used almost exclusively as maintenance therapy for the acute leukemias.

Tioguanine (thioguanine) is given by mouth to induce remission in acute myeloid leukemia.

CAPECITABINE

Indications: *see notes above.*

Side-effects: *see section 14.1*, important side-effect is hand foot syndrome.

Interactions: *see Appendix-2.*

Dose: 2500 mg/m^2 per day in 2 to 3 divided doses for 2 weeks followed by 1 week rest, to be taken with food

Proprietary Preparation
Xitabin*(Beacon)* Tab., 500 mg, Tk. 125/Tab.
Xeloda [I] *(Roche),* Tab., 500 mg, Tk. 350.29/Tab.

CYTARABINE

Indications: acute myeloid leukemia and, to a lesser extent, is used in chronic myelogenous leukemia and non-Hodgkin's lymphoma.

Cautions: *see section 14.1 and see notes above;* hepatic impairment.

Side-effects: *see section 14.1 and see notes above.*

Dose:

100-200 mg/m^2/day continuous IV infusion for 5-10 consecutive days – Induction or

100 mg/m^2 IV or SC twice a week for 5 days every 28 days.

MAINTENANCE DOSE:

- 40-50 mg/m^2 intrathecally every 4 days per week.
- 1,000 mg to 3,000mg/m^2 IV over 1 hour every 12 hours for up to 12 doses.

Proprietary Preparations
Cytarabine [I] *(Choongwa)* Inj. 100mg/5ml
Cytabin *(Beacon),* Inj. 100mg/5ml, Tk.180/amp

FLUDARABINE PHOSPHATE

Indications: B-cell chronic lymphocytic leukaemia, low grade Non-Hodgkin's lymphoma, acute myeloid leukaemia-Refractory and relapsing case.
Cautions: vaccination-during and after treatment with fludarabine phosphate , vaccination with live vaccines should be avoided. renal impairment.
Contraindication: hypersensitivity to the active substance or to any of the excipients;Renal impairment with creatinine clearance < 30 ml/ min;Hemolyticanemia;Pregnancy(Pregnancy Category D);Lactation; below 18 years of age
Side-effects: myelosuppression, opportunistic Infections, cough, fever, fatigue, weakness, nausea, vomiting, diarrhea, hematological disorders
Dose: 25 mg/m² body surface area given daily for 5 consecutive days every 28 days by the Intravenous route for up to 6 cycles.

Proprietary Preparation
Fludara[I] *(Genzyme),* Inj., 50mg/2ml, Tk. 7422/Vial

FLUOROURACIL[ED]

Indications: *see notes above*

Cautions *see section 14.1* and *see notes above*

Caution: in handling-irritant to tissues

Interactions: antibacterials such as metronidazole inhibit the metabolism

(increase toxicity), filgrastim possibly exacerbates neutropenia

Ulcer healing drugs such as cimetidine inhibits metabolism (increase plasma concentration)

Side-effects: same as the side-effects of cytotoxic drugs and *see notes above*

Dose: systemic - 500 mg/m^2 IV on days 1-5 every 4 weeks. 450-600 mg/m^2 IV weekly. 200-400 mg/m^2 IV daily as a continuous IV infusion. 1000 mg/m^2 IV daily for 4 days as a continuous IV infusion every 3-4 weeks

Intra-cavitary- 500-1000 mg for pericardial effusion. 2000-3000 for pleural or peritoneal effusion

Intra-arterial - 800-1200 mg/m^2 as a continuous infusion on days 1-4 followed by 600 mg/m^2 as a continuous infusion on days 5-21

Proprietary Preparation
Fluroxan *(Beacon),* Inj., 250 mg, Tk. 60.00/Vial; 500 mg, Tk. 100.00/Vial

GEMCITABINE

Indications: advanced pancreatic cancer: It may be useful in metastatic breast cancer

Cautions: *see section 14.1 and see notes above*

Side-effects: *see section 14.1* and *see notes above*

Dose: IV 1 g/m^2 over a period of 30 minutes once weekly for 7 weeks followed by 1 week rest. Subsequent courses of treatment are administered at the dose of 1 g/m^2 per week for 3 weeks followed by 1-week rest

Proprietary Preparations
Gemoxen *(Beacon),* Inj., (IV Infusion), 40mg/ml Tk. 5,000/25mlVial; Tk. 1,400/5ml Vial
Gemcitin *(Techno),* Inj., (IV Infusion), 40mg/ml, Tk. 7,287.50/25ml Vial; 200 mg/5ml, Tk.1,987.50/Vial
Gemcitabin medac[I] *(Medac)* Inj., (IV Infusion), 200mg/vial, Tk.2,482.81/Vial; 100mg/vial, Tk.12,411.03/vial
Gemzar*(Lilly)*Inj., (IV Infusion), 200mg/vial, Tk.2,478.34/Vial; 1g/vial, Tk.8671.92/vial
Gemcitabin HEXAL [I] *(Ebewe)* Inj., (IV Infusion), 40mg/ml, 975.00/5mlvial, Tk. 3,937/25ml
Gitrabin[I] *(Actavis)* Inj., (IV Infusion), 200mg/vial,Tk.1848.08/Vial;1gm/vial Tk.5850.50/vial

MERCAPTOPURINE

Indications: acute lymphatic leukaemia and acute non-lymphocytic leukemia. May be useful treatments for chronic myeloid leukaemia (CML), non-Hodgkin's lymphoma, polycythaemia vera, inflammatory bowel disease and psoriatic arthritis

Cautions: same as the side-effects of cytotoxic drugs *and see notes above;* reduce the dose in mild and moderate renal impairment; max. 2.5 mg in 24 hours and avoid in severe impairment

Interactions: *see Appendix-2.*

Side-effects: same as the side-effects of cytotoxic drugs and *see notes above*

Dose: oral dose is 70 to 100 mg/m^2/day (by mouth 2.5 mg/kg daily); 75% of the standard dose to be reduced if allopurinol is co-administered. A common IV dose is 500-1000 mg/m^2/day for 2-3 days. Dose adjustment of 6-MP administered by IV is not necessary with concomitant administration of allopurinol

Proprietary Preparations
Leukin *(Beacon)* Tab. 50 mg.Tk. 20/Tab.
Puri Nethol [I] *(GSK),* Tab. 50 mg, Tk.40.76/Tab.

METHOTREXATE [ED]

Indications: chroriocorcinoma, hydatidiform mole, all acute lymphocytic leukaemia, prophylaxis and treatment of meningeal lymphocytic leukemia, breast cancer, epidermal tumors of the head and neck, lung cancer, non-Hodgkin's lymphoma, T-Cell lymphoma, psoriasis and rheumatoid arthritis (second or third line treatment). Methotrexate may be a useful treatment for multiple myeloma, rhabdomyosarcoma and cancer of the bladder, brain, cervix, oesophagus,

kidney, ovary, prostate, stomach and testes

Cautions: *see section 14.1* and notes above; hepatic and renal impairment

Interactions: analgesics such as aspirin reduce the excretion, avoid concomitant use of azapropazone, diclofenac, ibuprofen, indomethacin, ketoprofen, meloxicam, naproxen and phenylbutazone and probably other NSAIDs increase the risk of toxicity *(see also Appendix-2 and notes below).*

Antibacterials such as co- trimoxazole and trimethoprim increase the antifolate effect of methotrexate, penicillin and sulphonamides decrease the excretion of methotrexate and increase the risk of toxicity.

Antiepileptics such as phenytoin increase the antifolate effect and thus increase the toxicity.

Antimalarial such as pyrimethamine increase the antifolate effect.

Ciclosporin increase the toxicity.

Corticosteroids increase the risk of haematological toxicity.

Uricosuric-probenecid reduces the excretion of methotrexate and increases the risk of toxicity.

Side-effects: same as the side-effects of cytotoxic drugs and notes above.

Dose: oral doses up to 40mg/m^2 are well absorbed. Parenteral doses vary from 20-40 mg/m^2 every 1 to 2 weeks to 200 to 500 mg/m^2 every 2 to 4 weeks

As adjuvant treatment for osteosarcoma, doses of 12,000 to 15,000 mg/m^2 have been given with leucovorin rescue the usual adult intrathecal dose is 10 to 15 mg in 7 to 15 ml of preservative free saline. Doses greater than 80 mg/week should be accompanied by leucovoria rescue

Proprietary Preparations

G-Methotrexate *(Gonoshasthaya),* Tab., 2.5mg, Tk. 4.00/Tab.
Methotrax *(Delta),* Tab., 10 mg, Tk. 15/Tab.; Tab. , 2.5 mg, Tk. 5.00/Tab.
Methox *(Popular),* Tab., 10 mg, Tk. 15.06/Tab.;Tab., 2.5 mg, Tk. 5.52/Tab.
Metorax *(Renata),* Tab., 2.5 mg, Tk. 5.50/Tab.
Mtrex*(Techno),* Inj., 50 mg, Tk 110/amp.
Trexonate *(Beacon),* Tab. , 10 mg, Tk. 15/Tab.; Tab., 2.5 mg, Tk. 5/Tab.; Inj., 50 mg, Tk.130/amp.

RALTITREXED

Indications: advanced colorectal cancer
Caution: hepatic and renal impairment
Contraindication: pregnancy and breast feeding

Side-effect: myclosppression and gastrointestinal disturbance

Interaction: *see Appendix-2*

Dose: *consult with oncologist*

Generic Preparation
Injection 2mg/vial

14.1.4 VINCA ALKALOIDS AND ETOPOSIDE

The **vinca alkaloids, Vincristine**, **vinblastine and vindesine** are used to treat the acute leukaemias, lymphomas and some solid tumors (eg. Breast and lung cancer). These naturally occurring or semisynthetic compounds are derived from periwinkle plant. Vincristine, vinblastine, vindesine, has been recently introduced. **Vinorelbine** are common vinka alkaloids used for different malignant conditions. They act by binding to tubulin and inhibit mitosis at metaphase. They are given by intravenous injection. The drugs are rapidly sequestered in cells, particularly the white blood cells and platelets. **Vincristine** has a longer life than other vinca alkaloids. The vinca alkaloids are relatively non-toxic. Myelosuppression is the dose limiting side-effect of vinblastine, vindesine and vinorelbine. **Vincristine** has a very mild myelosuppressive activity, but causes paresthesia (sensory changes) and neuromuscular abnormalities fairly frequently. Motor weakness can occur and increasing motor weakness calls for discontinuation of treatment with these drugs. **Vinblastin** is less neurotoxic but causes leucopenia, while vindesine has

both moderate myelotoxicity and neurotoxicity.

Etoposide is the semisynthetic derivative from mandrake root. It may be given orally or by slow intravenous infusions. **Etoposide** usually given daily for 3-5 days and courses should not be repeated more frequently than at intervals of 21 days. It has particularly useful activity in small cell carcinoma of bronchus, the lymphomas and testicular cancer. It may inhibit mitochondrial function of nucleoside transport, as well as to an effect on topoisomerase II. Toxic effects include myelosuppression and hair loss. Nausea and vomiting are also common.

ETOPOSIDE

Indications: particularly useful in lung cancer, testicular and ovarian cancer, gestational choriocarcinoma, Hodgkin's and non Hodgkin's lymphomas, acute myelogenous leukaemia, acute myelomonocytic leukaemia, Kaposi's sarcoma, neuroblastoma, Ewing's sarcoma, Wilm's tumor and rhabdomyosarcoma, cancer of breast, bladder and prostate.

Cautions : same as the side-effects of cytotoxic drugs and notes above

Contraindications: severe hepatic impairment

Side-effects: myelosuppression, alopecia, peripheral neuropathy; it is also irritant to tissue. Nausea and vomiting

Dose: 120-240 mg/m^2/day for 3 to 5 days; given orally

Proprietary Preparations
Topoxin *(Beacon),* Inj.,100mg/vial,Tk. 400/Vial
Eposid *(Techno),* Inj., 100 mg/vial, Tk.530/Vial
Eposin[I]*(Pharmachemie),* Inj., 100mg/vial, Tk. 584.07/Vial

VINBLASTINE SULPHATE [ED]

Indications: advanced Hodgkin's lymphomas and also to treat the carcinomas of bladder, breast, Kaposi's sarcoma and certain other malignant conditions, mycosis fungoides

Cautions: and *notes above;* hepatic impairment. Caution in handling; *(see under section 14.1)*

Contraindications: intrathecal injection

Side-effects: *see under section 14.1 and notes above;* irritant to tissue

Dose: 6 to 10mg/m^2 every 2 to 4 weeks in combination with other drugs

Generic Preparations
Injection 10mg/10ml vial

VINCRISTINE SULPHATE[ED]

Indications: vincristine is an essential part of combination chemotherapy regimens for ALL and play an important role in the treatment of both Hodgkin's and non Hodgkin's lymphomas and certain other tumors

Cautions: *Same as the side-effects of cytotoxic drugs and notes above;* hepatic impairment. Caution in handling

Contraindications: Intrathecal injection

Side-effects: same as the side-effects of cytotoxic drugs and notes above; irritant to tissue

Interactions: *see Appendix-2*

Dose: commonly used doses range from 0.5 to 1.4 mg/m^2 every 1 to 4 weeks. Continuous infusion regimens of 0.5 mg to 0.5 mg/m^2/day for 4 days have been used

Proprietary Preparations
Criston *(Beacon),* Inj., 1 mg/Vial, Tk. 350.00/Vial ; 2 mg/Vial, Tk. 580.00/Vial
Vincrist *(Techno),* Inj., 1 mg/Vial, Tk. 460.00/Vial
Vincristine[I]*(Phamachemie)* 1 mg/Vial, Tk. 371.95/Vial ; 2 mg/Vial, Tk. 526.92/Vial

VINORELBINE

Indications: *see notes above*

Cautions: *see section 14.1 and notes above*

Side effects: *see section 14.1 and notes above*

Interactions: *see Appendix-2.*

Dose: *Consult with oncologist*

Proprietary Preparations
Vinorelbin Sandoz[I] *(Ebewe),* Inj (I.V Infusion)10 mg/ ml, Tk. 1247.00/Vial; 4,370.00/5 ml, Vial
Vinorelbin Actavis[I] *(Actavis),* Inj(I.V Infusion), 10 mg/ ml, Tk. 10246.93/5mlVial;

14.1.5 OTHER ANTINEOPLASTIC DRUGS

Amscarine acts by intercalation with DNA and inhibition of nucleic acid synthesis. It is used for the induction and maintenance of remission in adult acute lymphatic leukaemias, particularly acute non-lymphoblastic leukaemia. Amsacrine has cardiotoxic effects similar to those of doxorubicin and it is poorly absorbed following oral administration. Side-effects include bone marrow depression and mucositis; cardiac arrhythmia may occur especially in patients with pre-existing hypokalaemia.

Altretamine is recently been licensed for the treatment of advanced ovarian cancer where other regimen has failed. Altretamine is given orally and should be discontinued if dose reduction fails to stabilize symptoms of neurological toxicity. Prolonged or high dose therapy may be associated with peripheral and central neurotoxicity and regular neurological examination is to be recommended. Other side-effects include rash, renal and hepatic toxicity.

Crisantaspase is the enzyme asparaginase produced by *Erwinia chrysanthemi*. It is given IM or S/C exclusively in Acute Lymphoblastic Leukaemia. Side-effects include nausea and vomiting and can cause anaphylactic reactions, CNS depression, and liver damage.

Erlotinib is used for treatment of patients with metastatic or locally advanced non-small cell lung cancer who have failed at least one previous round of chemotherapy. It also is used for maintenance of NSCLC that has not progressed after four cycles of platinum-based first line chemotherapy. **Erlotinib** is combined with **gemcitabine** to treat advanced unresectable metastatic prostate cancer and for pancreatic cancer. It is a reversible tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor
Note: Erlotinib monotherapy is not recommended for maintenance treatment in people with locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first line chemotherapy.
Everolimus is a protein kinase inhibitor. It is used to treat advanced renal cell carcinoma that has already been treated unsuccessfully with other medications. It is also used to treat a certain type of advanced breast cancer that has already been treated with at least one other medication.
Imatinib is a protein tyrosine kinase inhibitor, which is licensed for the treatment of chronic myeloid leukaemia, in chronic phase after failure of interferon alfa, or in accelerated phase or in blast crisis. The most frequent side effects of imatinib are nausea, vomiting, diarrhea, oedema, muscle pain and headache.

Nilotinib a tyrosine kinase inhibitor, used for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase and also for the treatment of chronic phase and accelerated phase in adult patients resistant to or intolerant to prior therapy that included imatinib.
Sorafenib is a tyrosine kinase inhibitor. Sorafenib is used to treat advanced renal cell carcinoma Sorafenib is also used to treat hepatocellular carcinoma that cannot be treated with surgery and a certain type of thyroid cancer that has spread to other parts of the body and cannot be treated with radioactive iodine.

Sunitinib Sunitinib is a type of targeted therapy known as a tyrosine kinase inhibitor. This drug is used to treat advanced kidney cancer. It is also used in gastrointestinal stromal tumor , after failure of imatinib, and for the treatment

of unresectable or metastatic pancreatic neuroendocrine tumour .

ALTRETAMINE

Indications: *see notes above*

Cautions: hepatic and renal impairment; to be careful in handling (*see section 14.1 and notes above*)

Side-effects: *see section 14.1 and notes above*

Dose : 260 mg/m^2/day in 4 divided dose (after meals and at bedtime) for 14 days to 21 days of a 28 day cycle; given for up to 12 cycle

Generic Preparation
Capsule 100mg

BORTEZOMIB

Indication: relapsed multiple myeloma and mantle cell lymphoma
Cautions: pregnancy, liver disease, kidney disease
Contraindication: pregnancy
Side-effects: peripheral neuropathy, myelosuppression, neutropenia, thrombocytopenia, asthenia.
Dose: 1.3 mg/m^2 (with or without dexamethasone) administered by intravenous bolus on days 1,4,8, and 11 of a 21-day cycle for a maximum of eight cycles in heavily pretreated patients with relapsed/refractory multiple myeloma.

Generic Preparation
Injection 3.5mg/vial

DACARBAZINE AND TEMOZOLOMIDE

Dacarbazine is a cell cycle non-specific antineoplastic which may function as an alkylating agent after it has been activated in liver and is used mainly to treat metastatic malignant melanoma, in combination regimen for the treatment of soft tissue sarcoma, Hodgkin's disease. It is given intravenously. The predominant side-effects are myelosuppression & severe nausea, vomiting.

Temozolomide is structurally related to decarbazine and is licensed for the second line treatment of malignant glioma. It is an oral preparation.

DACARBAZINE

Indication: *see notes above.*

Caution: same as the side-effects of cytotoxic drugs and notes above; hepatic and renal impairment ,pregnancy, breast feeding

Side-effects: same as the side-effects of cytotoxic drugs and notes above; rarely liver necrosis due to hepatic vein thrombosis; irritant to skin and tissues

Dose: it is given IV in doses of 150-250 mg/m^2/day for 5 days, to be repeated at intervals of 4 weeks, or 250 mg/m^2 body surface daily for 5 days, to be repeated at intervals of 3 weeks

Proprietary Preparations
Decarbazine (I) *(Mayane),* Inj. 200 mg/20 ml. Tk.1126.96/20ml vial
Decarbazine Medac(I) *(Medac*), Inj., 200mg/ vial,Tk.7962.35/vial

ERLOTINIB

Indications: *see notes above*
Cautions: *see section 14.1* and notes above;.renal impairment; hepatic impairment; pregnancy & breast feeding.
Side-effects: same as the side-effects of cytotoxic drugs and notes above.
Dose : non-small cell lung cancer, 150 mg once daily. Pancreatic cancer, 100 mg once daily in combination with gemcitabine

Proprietary Preparations
Erlonix *(Beacon),* Tab. , 100 mg, Tk. 600.00/Tab.; 150 mg, Tk. 750.00/Tab.
Tarceva(I) *(Roche),* Tab., 150 mg, Tk. 5,091.13/Tab.; 100 mg, Tk. 4,168.21/Tab.
Tercenib *(Techno),* Cap. , 150 mg, Tk. 750.00/Cap.; 100 mg, Tk. 650.00/Cap.

EVEROLIMUS

Indications: advanced kidney cancer, prevention of organ rejection after renal and kidney transplant, breast cancer in post-menopausal women with advanced hormone-receptor positive
Cautions: hepatic impairment, renal impairment, pregnancy, breast feeding
Side effects: change in ability to taste food, dry mouth, weakness, difficulty falling asleep, nose bleed, muscle cramps
Dose: renal cell carcinoma, neuroendocrine tumours of pancreatic origin, hormone-receptor-positive breast cancer. ADULT over 18 years, 10mg once daily
Note: for subependymal giant cell astrocytoma or renal angiomyolipoma associated with tuberous sclerosis complex; *consult product literature*

Proprietary Preparations
Afinitor[I] *(Novartis),* Tab., 5 mg, Tk. 5813.00/Tab.; 10 mg, Tk. 8943.00/Tab.;
Certican[I] *(Novartis),* Tab., 0.25 mg, Tk. 125.00/Tab.; 0.50 mg, Tk. 250.00/Tab
Xevirol*(Beacon),* Tab., 5 mg, Tk. 66.60/Tab.; 10 mg, Tk. 100.00/Tab.;

GEFITINIB

Indication: Non-small cell lung cancer (NSCLC).
Cautions: breast-feeding, interstitial lung disease (ILD), hepatotoxicity and liver impairment
Contraindication: pregnancy and breast-feeding (must be discontinued while receiving Gefitinib therapy)
Side effects: anorexia mild or moderate, conjunctivitis, blepharitis, and dry eye, corneal erosion, Keratitis (0.12%), haemorrhage, diarrhoea, vomiting, hepatobiliary disorders, skin reactions, nail disorder, cutaneous vasculitis, proteinuria, cystitis
Dose: 250mg tablet once a day

Proprietary Preparation
Gefinix *(Beacon)*, Tab. 250 mg, Tk.250/Tab.

HYDROXYCARBAMIDE/HYDROXYUREA

Hydroxycarbamide (hydroxyurea) is a urea analogue that inhibits ribonucleotide reductase, thus interfering DNA. The drug is given orally & is mainly licensed for the treatment of chronic myeloid leukaemia. It has the usual unwanted effects; bone marrow depression being significant.

HYDRPXY CARBAMIDE

Indication: *see notes above*
Cautions, Side-effect : *see section 14.1*
Contra-indications: pregnancy & breast feeding
Dose: *cosult with oncologist*

Proprietary Preparations:
Hydrea[I]*(Squibb),*Cap.500mg, Tk.19.83/Cap
Hydronix*(Beacon),*Cap. 500mg, Tk.15.00/Cap

IMATINIB

Indication: *see notes above.*
Cautions: cardiac disease; risk factors for heart failure; history of renal failure; monitor for fluid retention; monitor liver function ; monitor growth in children *(see section 14.1)*

Side-effects: *see section 14.1* and notes above.

Dose: 400 mg/day till the disease persists (Literature advised for at least one year)

Proprietary Preparations
Imanix *(Beacon),* Tab. , 100 mg, Tk. 100.00/Tab.; 400 mg, Tk. 375.00/Tab.
Enliven *(Orion),* Cap, 100 mg, Tk. 125.47/Cap.
Glivec[I] *(Novartis),* Cap. 100 mg, Tk. 1666.00/Cap.

LAPATINIB

Indications: metastatic breast cancer and other solid tumors. It is used in combination therapy for HER2-positive breast cancer.
Cautions: hepatotoxicity, pregnancy category D, renal impairement

Contraindication: same as that of cautions
Side effects: fast or pounding heart beats, extreme dizziness or tired feeling, feeling like you might pass out, severe diarrhea, dry cough, feeling short of breath, white patches or sores inside mouth or on lips, nose bleeding (*see section 14.1)*
Dose: 1,250 mg given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2 /day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle.

Proprietary Preparation
Tykerb[i] *(GSK),*Tab., 250 mg TK.356.59/Tab

NILOTINIB

Indications: *see notes above*
Cautions: prolongs the QT interval; concomitant use of drugs that prolong QT interval; hypokalemia, hypomagnesemia, or long QT syndrome
Side effects: headache with chest pain and severe dizziness, fainting, fast or pounding heartbeats; fever, chills, body aches, flu symptoms, sores in mouth and throat; blood in urine or stools; severe pain in upper stomach spreading to back; QT- interval prolongation; hypertension, oedema
Dose: consult product literature

Proprietary Preparation
Tasigna[i] *(Novartis),* Cap. 200 mg, Tk.3040/Cap.

PAZOPANIB

Indications: renal cell carcinoma and soft tissue sarcoma
Cautions: hypertension, including hypertensive crisis , thrombotic microangiopathy; thrombocytopenic purpura, hemolytic uremic syndrome; decreased LVEF and congestive heart failure
Contraindications: Same as that of cautions, not recommended in patients with severe hepatic impairment
Side effects: changes in hair colour, hypertension which usually occurs during the first few weeks of treatment, appetite loss, hyperglycaemia, hypocalcaemia, hypomagnesemia, hypophosphatemia, increased AST, ALT and protein in the urine, oedema, rash, fatigue, and myelosuppression.
Interactions:*see Appendix -2*
Dose: 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal). Baseline moderate hepatic impairment – 200 mg orally once daily.

Proprietary Preparation
Votrient[i] **(***GSK)* Tab.,800 mg Tk.625.69

SORAFENIB

Indications: *see notes above*
Caution: major surgical procedures, cardiac ischaemia, susceptibility to QT-interval prolongation, hepatic impairment, pregnancy and breast-feeding
Side-effects: decreased blood flow to the heart and heart attack, bleeding problems,high blood pressure, hand-foot skin reaction,Interstitial lung disease reversible thyroid dysfunction and Stevens-Johnson syndrome
Dose: ADULT over 18 years, 400 mg twice daily

Proprietary Preparation
Soranix *(Beacon),*Tab. 200mg,Tk.300.00/Tab.

SUNITINIB

Indications: *see notes above*
Cautions: increased risk of bleeding; monitor for thyroid dysfunction; congestive heart failure, high blood pressure, QT-interval prolongation; consider dental check-up before initiating treatment, pregnancy and breast-feeding
Side-effects: fatigue, hand-foot skin reaction, hypertension, paraesthesia, hypothyroidism, arthralgia, increased lacrimation, epistaxis

Dose: 50 mg once daily for gastrointestinal stromal tumor and advanced renal cell carcinoma

Proprietary Preparation
Sunitix *(Beacon),* Cap. 50 mg, Tk. 2000/Cap.

TEMOZOLOMIDE

Indication: malignant glioma.

Cautions: same as the side-effects of cytotoxic drugs and notes above; hepatic and renal impairment; caution in handling
Contraindication: CHILD under 3 years not recommended

Side-effects: *see notes above*
Dose: consult product literature

Proprietary Preparations:
Temonix *(Beacon),* Cap. , 100 mg, Tk. 600.00/Cap.; 250 mg, Tk. 1,300.00/Cap.
Zolomide *(Techno),* Cap. , 100 mg, Tk. 650.00/Cap.; 250 mg, Tk. 1,500.00/Cap

PLATINUM COMPOUNDS

The platinum compounds are complexes of platinum with ligands which can be displaced by nucleophilic (electron rich) atoms to form strong bonds with covalent characteristics. Thus, like the alkylating agents, the platinum agents form strong chemical bonds with thiol sulfurs and amino nitrogens in proteins and nucleic acids.
Cisplatin requires a "Day-care setting" and is given intravenously. It is of value in patients with metastatic germ cell tumors (Teratoma, seminoma). It can also be used in bladder, lung, upper GIT and ovarian cancer though for ovarian cancer **carboplatin** is more preferable. **Cisplatin** requires intensive intravenous hydration and treatment may be complicated by severe nausea and vomiting. This is generally toxic giving rise to nephrotoxicity, ototoxicity, peripheral neuropathy.
Carboplatin has activity equivalent to that of cisplatin but used specially in ovarian cancer and lung cancer (Particularly small cell type). It is administered intravenously on an out patient basis and it is better tolerable than **cisplatin.** The dose of carboplatin is determined according to the renal function rather than the body surface area. Though the myelosuppression is more severe than cisplatin but the nephrotoxicity or ototoxicity with carboplatin is less severe.
Oxaliplatin is administered intravenously for the treatment of metastatic colorectal cancer in combination with flourouracil and folinic acid. Along with sensory peripheral neuropathy which id dose limiting other side effects eg. GIT disturbance, ototoxicity, myelosuppression are also common. Manufacturers advise for close monitoring of the renal functions.

CARBOPLATIN

Indications: *see notes above*
Cautions: *see section 14.1* and notes above; renal impairment
Interactions: antibacterials such as aminoglycosides, vancomycin and capreomycin increase the risk of nephrotoxicity and possibly ototoxicity; diuretics increase the risk of nephrotoxicity and ototoxicity.
Side-effects: *see section 14.1 and notes above*
Doses: common IV dose is 360 to 400 mg/m^2 every 4 weeks. Doses of 400 to 550 mg/m^2 have been given. Carboplatin can also been administered in higher doses (e.g. 1500 mg/m^2) in combination with other antineoplastic drugs
The dose of carboplatin, based on target AUC, is calculated using the following formula:
Dose (total mg)=Target AUC X (GFR + 25)
The patient's creatinine clearance, in ml/minute, is often used in place of GFR. A target AUC of 6 to 7 is often used depending on the patient's prior therapies and drug(s) that will be used in combination with carboplatin. A target AUC of 4 to 6 may be appropriate for patients who have received extensive prior treatment, and a higher target AUC may be appropriate for previously untreated patients

Proprietary Preparations
Carboplat *(Beacon),* Inj.,(I.V infusion) 10mg/ml, Tk. 1,400.00/15mlVial ; Tk. 3,800.00/45 ml Vial
Carbotin *(Techno),* Inj. (I.V infusion)10mg/ml, Tk. 4,637.50/45ml; Tk.1,550.00/15mlVial
Carboplatin HEXAL[I] *(Hexel),* Inj. (I.V infusion) 10mg/ml ,Tk. 1,166.00/15 ml Vial; Tk. 3,069.00/45 ml Vial; Tk. 423.00/5 ml Vial
Carboplatin sindan[I] *(Sindan)* Inj. (I.V infusion) 10mg/ml, Tk.4146.14/45ml vial; Tk. 5156.47/60ml vial

CISPLATIN[ED]

Indications: *same as notes above*
Cautions: *see section 14.1* and notes above; renal impairment; to be monitored renal function and haemoglobin parameter
Interactions: antibacterials such as aminoglycosides, vancomycin and capreomycin increase the risk of nephrotoxicity and possibly ototoxicity; diuretics increase the risk of nephrotoxicity and ototoxicity
Side-effects*: see section 14.1 and notes above*
Dose: doses may vary from 20 to 40 mg/m^2/day for 3 to 5 days every 3 to 4 weeks or from 20-120 mg/m^2 given as a single dose every 3-4 weeks intra peritoneal dose of 100 to 270 mg/m^2 have been given in combination with IV sodium thiosulfate

Proprietary Preparations
Cesalin *(Techno),* Inj. (I.V infusion) , Tk. 225.00/10mgVial;Tk. 1,060.00/50mgVial
Cisplatin HEXAL PI[I] *(Hexel),* Inj. (I.V infusion) Tk. 313.00/20 ml Vial ; 50 mg/100ml, Tk. 987.00/100 ml Vial
Platinex *(Beacon),* Inj. (I.V infusion) , Tk. 250.00/10mgVial; Tk. 815.00/50mgVial
Sinplatin[I] *(Actavis),* Inj. (I.V infusion) 50 mg/vial,Tk.1114.47/50mlVial;Tk.370.00/10mlvial

OXALIPLTIN

Indications: metastatic colorectal cancer in combination with FU and folinic acid
Cautions: renal impairment
Contraindications: peripheral neuropathy and functional impairment
Side-effects: *see section14.1 and notes above*
Dose: consult with oncologist

Proprietary Preparations
Eloxatin[I] *(Aventis),* Inj. 50 mg/Vial, Tk. 6230.74/Vial
Oxaliplatin medac[I] *(Medac***)** , Inj., 100 mg/vial, Tk. 5387.32/vial
Oxalotin *(Techno),* Inj., 100 mg/vial, Tk. 7,900.00/vial ;50 mg/vial,Tk. 5,962.50/vial
Xaloplat *(Beacon),* Inj., 100 mg/vial, Tk. 5,500.00/vial; 50 mg/vial, Tk. 3,000.00/vial
Sindaoxplatin[I] *(Sindan***),** Inj., 50 mg/Vial, Tk. 4377.00/vial

PROCARBAZINE[ED]

Procarbazine is mainly used in the treatment of Hodgkin's disease, with other combination eg. MOPP (Mustine, Oncovin, Procarbazine and Predniso-lone). It inhibits DNA and RNA synthesis and interferes with mitosis at interphase. Its effects may be due to the production of active metabolites. It is given orally. Usual side-effects includes nausea, hypertension, tachycardia, diplopia, photophobia, myelosuppression and skin rash Immediate cessation of treatment is required if rash appears.

PROCARBAZINE [ED]

Indications: *same as notes above.*
Cautions: *see section 14.1*and notes above*;* renal impairment; reduce the dose in moderate impairment
Interactions: alcohol ingestion may cause a disulfiram like reaction; it can cause hypertension, because it is a weak MAOI. *see also Appendix-2*
Side-effects: *see section 14.1* and notes above
Dose : initially 50 mg daily, increased by 50 mg daily to 250-300 mg daily, in divided doses; maintenance (on remission) 50-150 mg daily to cumulative total of at least 6g

Generic Preparation
Capsule 50 mg.

TAXENES

Docetaxel, though recently been licensed for initial chemotherapy with doxorubicine for advanced breast cancer, it's main use was in the treatment of advanced or metastatic breast cancer and non-small cell lung cancer. It is the second generation taxene. It acts by enhancing formation and stabilization of microtubules. Antineoplastic effect may result from non-functional tubules or altered tubulin microtubule equilibrium. Mitotic arrest is seen and is associated with accumulated polymerized microtubules. Dose limiting factor for Docetaxel is neutropenia. Severe (grade 4) neutropenia is common among patients who have neutropenic fever. Nausea and vomiting are common, but brief. Fluid retention syndrome is common and cumulative. It can be reduced to occasional frequency by prophylactic steroids. Severe hypersensitivity reactions with flushing, hypotension with or without dyspnoea. pre-medication with dexamethasone, 8 mg PO twice daily for 5 days starting 1 day before docetaxel limits the frequency and severity of hypersensitivity.

Paclitaxel is the first drug of the new class known as Taxanes. It is given intravenous infusion. Paclitaxel along with carboplatin or cisplatin is the treatment of choice for ovarian cancer (NICE guideline). Paclitaxel is also used in second line treatment of metastatic breast cancer. Some source also claim for it's usefulness in non-small cell lung cancer. Routine pre medication with a corticosteroid and an antihistamine to prevent severe hypersensitivity reaction is recommended. Hypersensitivity reactions may occur rarely; although more commonly only bradycardia or asymptomatic hypotension may occur. Along with these some complains of myelosuppression, peripheral neuropathy and cardiac conduction defects with arrhythmias (which are nearly asymptomatic). It also causes alopecia, muscle pain, nausea and vomiting from mild to moderate.

CABAZITAXEL

Indications: In combination with prednisone, for the treatment of patients with hormone-refractory metastatic prostate cancer (mHRPC) previously treated with a docetaxel-containing treatment regimen

Cautions: severe hypersensitivity can occur and may include generalized rash/ erythema, hypotension and bronchospasm. Discontinue cabazitaxel immediately if severe reactions occur and administer appropriate therapy

Contraindications: in patients with neutrophil counts of ≤1,500 cells/mm3; a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80

Side-effects: The most common (_10%) grade 1–4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, dyspepsia, cough, arthralgia, and alopecia. The most common (_5%) grade 3–4 adverse reactions in patients who received cabazitaxel were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia

Dose 25 mg/m² as a 1-hour IV every 3 weeks, in combination with oral prednisone 10 mg administered daily

Proprietary Preparation

Jevtana[I] *(Sanofi),* Inj., 60 mg/1.5 ml, Tk. 142687/Vial

DOCETAXEL

Indications: breast cancer, non-small cell lung cancer, gastric cancer, head and neck cancer, ovarian cancer; *see also the notes above*

Cautions: same as the side-effects of cytotoxic drugs; hepatic impairment, monitor liver function - dose reduced according to liver enzymes; avoid in severe hepatic impairment

Contraindications: patients with serious bone marrow depression, complication of infection, suspecting of infection
Interactions: erythromycin, ketoconazole, ciclosporin may cause possible interactions; *see also Appendix-2*
Side-effects: same as the side-effects of cytotoxic drugs
Dose: ADULT dose is 60-100 mg/m² (body surface area), IV drip infused over 1 hour once a day at intervals of 3-4 weeks

Proprietary Preparations
Docexan *(Beacon),* Inj., 20 mg/0.5 ml, Tk. 3,200.00/Vial**;**80 mg/2 ml, Tk. 11,000.00/Vial
Docetex *(Techno),* Inj., 20 mg/0.5 ml, Tk. 5,000.00/Vial ; 80 mg/2 ml, Tk. 18,000.00/Vial
Taxotere(I) *(Sanofi),* Tab. 20 mg, Inj. Tk. 6991.00/Vial

PACLITAXEL

Indications: primary ovarian cancer (advanced or residual disease following laparotomy) in combination with cisplatin; metastatic ovarian cancer where standard platinum-containing therapy has failed; advanced or metastatic breast cancer (in combination with trastuzumab) when an anthracycline not appropriate; metastatic breast carcinoma where standard anthracycline-containing therapy has failed or is inappropriate; non small cell lung cancer (in combination with cisplatin) when surgery or radiation therapy not appropriate
Cautions: see section 8.1 and notes above.
Interactions: *see Appendix-1*
Contra-indications: *see notes above*
Side-effect: *see notes above.*

Proprietary Preparations
Paclitaxel Actavis(I) *(Actavis),* Inj(I.V Infusion), 6mg/ ml, Tk. 5081.88**/**16.7 ml Vial; Tk.13855.01/43.33ml vial
Paclitaxel medac(I) (*Medac)* Inj(I.V Infusion), 300 mg/Vial,Tk/13,552.94/Vial; 100 mg/16.7ml, Tk. 6,707.25**/**Vial; 30 mg/5 ml, Tk.2,647.69/Vial
Paclitaxel Sandoz(I) *(Ebewe),* Inj(I.V Infusion), 100 mg/16.7 ml, Tk. 2,826.00**/**Vial; 30 mg/5 ml, Tk. 1,205.00/Vial
Paclitex *(Techno),* Inj(I.V Infusion), 6 mg/ml, Tk. 2,650.00/5mlVial ; Tk. 11,500.00/50mlVial
Xelpac *(Beacon),* Inj(I.V Infusion), 100mg/Vial, Tk. 4,500.00/Vial ; 30 mg/Vial, Tk. 1,700.00/Vial; 300 mg/Vial, Tk. 9,900.00/Vial

TOPOISOMERASE I INHIBITORS

Irinotecan and **topotecan** are the recently introduced anticancer drugs which inhibit topoisomerase I, an enzyme involved in DNA replication. In addition to dose limiting myelosuppression, side-effects of irinotecan and topotecan include gastrointestinal effects, asthenia, alopecia and anorexia.
Irinotecan, a semisynthetic derivative of camptothecins is potent inhibitor of topoisomerase I, an enzyme essential for effective replication and transcription, is given by intravenous infusion in carcinoma of the colon or rectum in combination with fluorouracil and folinic acid or when flouorouracil failed.
Topotecan is given by intravenous infusion in metastatic ovarian cancer when first line or subsequent therapy has failed.

IRINOTECAN HYDROCHLORIDE

Indications: carcinoma of the colon or rectum in combination with fluorouracil
Cautions: *see section 14.1* and notes above; raised serum bilirubin concentration. Avoid in severe hepatic impairment
Contraindications: chronic IBS, bowel obstruction, plasma bilirubin concentration more than 1.5 times the upper limit of reference range; avoid conception for at lest 3 months after cessation of treatment
Side-effects: same as the side-effects of cytotoxic drugs and notes above; acute cholinergic syndrome and delayed diarrhoea
Dose : 350 mg/m^2 administered as an IV infusion over a 30 to 90 minute period every three weeks as single agent in 5FU refractory cases, and 180 mg/m^2 in combination with 5FU and folinic acid as first line therapy

Proprietary Preparations
Campto(I) *(Pfizer),* Inj. (IV infusion), 20 mg/ ml, Tk. 11,957.63/5 ml Vial; Tk. 4985.59/5 ml Vial
Irinotecan Sandoz(I) *(Ebewe),* Inj.(I.V infusion), 20mg/ ml, Tk. 1,398.00/5 ml Vial ; 100 mg/5 ml, Tk. 2,800.00/5 ml Vial
Irinotecan medac(I) *(Medac)*, Inj.(IV infusion), 100 mg/5 ml, Tk. 9,101.42/Vial ; 40mg/2 ml, Tk. 4,137.01/Vial
Irinotesin(I)*(Actavis)*, Inj. (IV infusion), 20mg/ml, Tk.6326.38/5mlvial; Tk.2588.06/2ml vial

TOPOTECAN

Indications: metastatic
Cautions: renal impairment, pregnancy and breast feeding.
Contraindications: *see notes above,* hepatic impairment, pregnancy and breast feeding
Side-effects: *see notes above and see sec.14.1*
Dose:1.5 mg/m^2/day for 5 days as single agent

Generic Preparations
Injection 1mg/ml, 4ml vial

TRASTUZUMAB

Trastuzumab is a monoclonal antibody that has recently introduced for the treatment of metastatic breast cancer in patients whose tumours overexpress the human epidermal growth factor receptor 2 (HER2). Trastuzumab treatment should be reserved for patients who have previously received appropriate chemotherapy or in whom such treatment is inappropriate. Administration should be monitored by a specialist. As trastuazumab is a monoclonal antibody and is highly selective, it is important to done the receptor study (ER, PR, and HER2) before prescribing trastazumab. Suitable patient selection is important for using Trastuzumab. The combination of **trastuzumab** with **taxanes** improves the efficacy in a wide range. Trastuzumab should only be used in patients whose tumors have HER2 over expression

TRASTUZUMAB

Indication: as a single agent is indicated for the treatment of metastatic breast cancer in HER2 over expressions
Cautions: history of hypertension, pregnancy
Contraindications: severe dyspnoea and breast-feeding
Side-effects: chills, fever, anaphylaxis, urticaria, angioedema, gastrointestinal symptoms, asthenia, arthralgia, hypotension
Dose : 4 mg/kg IV as loading dose over 90 min followed by 2 mg/kg over 30 min weekly

Proprietary Preparations
Herceptin(I) *(Roche)*, Inj., 440 mg/vial, Tk. 208766.54/Vial
Trastunix *(Beacon),* Inj., 440 mg/Vial, Tk. 80,000.00/Vial
Zumab *(Techno),* Inj., 440 mg/Vial, Tk. 1,26,000.00/Vial

TRETINOIN

Tretinoin is licensed for the induction of remission in acute promyelocytic leukaemia. It is used in previously untreated patients as well as in those who have relapsed after standard chemotherapy or who are refractory to it. The efficacy of All Trans Retinoic acid (ATRA) in the treatment of Acute Promyelocytic Leukemia (APL) was first demonstrated in 1988 in China & then in France, the USA & Japan. In APL patients there is a translocation between chromosomes t(15, 17). In patient with this (15;17) chromosome translocation, the trans retinoic acid has been used to induce remission by causing differentiation of the malignant clone. In many APL patients (25%) treated with vesanoid a syndrome occurs known as RAS. The pathogenesis of RAS & the relationship to the other biologic effects seen with Vesanoid (RA) remains unclear. The description of a similar symptom complex in patients with APL who have not received RA has raised the possibility that this syndrome is directly related to the disease process. At the first onset of RAS, a short course of high dose steroid (Dexamethasone 10

mg iv, twice a day, for three or more days) can effectively stop progression of RAS. Vesanoid is highly teratogenic; so contraindicated in pregnancy, and Nursing mothers. In many APL patient treated with vesanoid a syndrom occurs known as RAS. If untreated, this may be fatal.

TRETINOIN

Indication: acute promyelocytic Leukaemia.
Caution: monitor Retinoic Acid Syndrome
Interactions: *see Appendix-2*
Contraindication: pregnancy & Nursing mother as it is highly teratogenic
Side-effects: RAS, acute respiratory distress, edema, hepatic or renal failure
Dose: adult and child 45 mg/m2 daily in two divided doses. Duration of treatment is 90 days

Proprietary Preparation
Vesanoid[I] *(R.P. Scherer),* Cap. 10 mg, Tk. 190.54/Cap.

BEVACIZUMB

Indications: used in combination with I.V 5FU based chemotherapy, first line treatment of patient with metastatic carcinoma of colon and rectum
Contraindications: should not be indicated for at least 28 days following major surgery; the incision should be fully healed prior to initiation of the chemotherapy
Side effects: serious and in some case fatal hemorrhage has occurred with non-small cell lung cancer treated with chemotherapy; gastrointestinal perforation and impaired wound healing; hypertensive crisis, nephritic syndrome, congestive heart failure
Dose: 5mg/kg given once every 14 days as an IV infusion until disease progression is detected

Proprietary Preparations
Avastin[I] *(Roche),* Inj., 100 mg/4 ml, Tk. 56,444.80/4 ml Vial
Bevastim *(Beacon),* Inj., 100 mg, Tk. 20,000/Vial

14.2. DRUGS AFFECTING THE IMMUNE RESPONSE

IMMUNOSUPPRESSANT THERAPY

Immunosuppressants are used to suppress rejection of transplanted organs and tissues (kidney, bone marrow etc.); to suppress graft-versus-host disease in bone marrow transplants; to treat a variety of chronic inflammatory and auto-immune diseases which includes ITP, some forms of Haemolytic Anaemia, GN, Myasthenia Gravis, SLE, Rheumatoid Arthritis, etc.

PREGNANCY: Transplant patients maintained with azathioprine should not discontinue it on becoming pregnant; because there is no evidence of azathioprine's teratogenicity. There is less experience of ciclosporin in pregnancy but it does not appear to be any more harmful than azathioprine. Tacrolimus and mycophe-nolate mofetil are contraindicated in pregnancy by the manufacturers themselves.

14.2.1 ANTIPROLIFERATIVE IMMUNOSUPPRESSANTS

Azathioprine is used widely by the transplant recipients and to treat a number of autoimmune diseases, usually when corticosteroid therapy alone fails to provide adequate control. The predominant toxic effect is myelosup-pression, although hepatic toxicity is also very common. In term therapy the blood counts must be monitored to check the myelosuppression. The drug is metabolized to give mercaptopurine, a

purine analogue that inhibits DNA synthesis. Both cell mediated and antibody-mediated immune reactions are depressed by this drug since it inhibits clonal proliferation in the induction phase of the immune response by a cytotoxic action on dividing cells.

Mycophenolate mofetil has a more selective mode of action than azthioprine. It is licensed for the prophylaxis of acute rejection in renal and cardiac transplantation when used in combination with ciclosporin and corticosteroids though the risk of opportunistic infection and blood disorder such as leucopenia is higher.

Cyclophosphamide and **chlorambucil** are less commonly prescribed as immunosuppressants.

AZATHIOPRINE

Indications: transplant recipient and auto immune diseases

Cautions: monitor blood count weekly for 4 weeks; thereafter reduce frequency of monitoring to at least every three months; the doses to be reduced in hepatic and renal impairment; elderly patients and pregnancies

Interactions: *see Appendix-2.*

Contraindication: hypersensitivity to azathioprine or mercaptopurine

Side-effects: hypersensitivity reactions, dose related bone marrow suppression, nausea hair loss and increased susceptibility to infections and colitis in patients also receiving corticosteroids

Dose: *by mouth,* by intravenous injection over at least 1 minute (followed by 50 ml sodium chloride intravenous infusion) or by intravenous infusion;

Autoimmune conditions: 1-3 mg/kg daily, adjusted according to response;

Suppression of transplant rejection, initially up to 5 mg/kg then 1-4 mg/kg daily according to response

Proprietary Preparations

G-Azathiopine *(Gonoshasthaya),* Tab., 50mg, Tk. 8.00/Tab.

Imuran[I] *(GSK),* Tab., 50 mg, Tk. 1,244.64/Tab.

MYCOPHENOLATE MOFETIL

Indications: prophylaxis of acute renal, cardiac or hepatic transplant rejection

Cautions: blood count every week for 4 weeks then twice a month for 2 months then every month in the first year elderly patients, risk of haemorrhage, ulceration and perforation; delayed graft function; susceptibility to skin cancer

Interactions: anion exchange resin colestyamine reduces absorption; antacids reduce absorption of the drug

Contraindications: breast-feeding, pregnancy (exclude before starting and avoid for 6 weeks after discontinuation)

Side-effects: gastrointestinal discomforts, hypertension, edema, dyspnoea, cough, rhinitis, dizziness, insomnia, headache, tremor, infection, leucopenia, anaemia, thrombocytopenia, leucocytosis, polycythemia, electrolytes disturbances, hyperglycemia, renal damage, haematuria, acne, lymphoproliferative disease

Dose: renal transplantation: by mouth, 1 g twice daily starting within 72 hours of transplantation or by intravenous infusion, 1 g twice daily within 24 hours of transplantation for up to maximum 14 days

Cardiac transplantation: by mouth 1.5 g twice daily within 5 days of transplantation.

Note: Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection, inexplicable bruising or bleeding

Proprietary Preparations

Cellcept[I] *(Roche),* Tab., 500 mg, Tk. 141.76/Tab.

Mycophenolat-Mofetil *(Novartis),* Tab., 500 mg, Tk. 67.46/Tab.

Mycophenolat-Mofetil sandoz[I] *(Sandoz),* Tab., 500 mg, Tk. 67.46/Tab.

Mycotil *(Techno),* Tab., 500 mg, Tk. 55.00/Tab.

Myfortic[I] *(Novartis),* Tab., 180 mg, Tk. 79.00/Tab.; 360 mg, Tk. 157.00/Tab.

Phenocept *(Renata),* Tab., 500 mg , Tk. 65.00/Tab.

14.2.2 CORTICOSTEROIDS AND OTHER IMMUNOSUPPRESSANTS

Corticosteroids have great clinical value in the treatment of acute lymphoblastic leukemia, malignant lymphomas etc. It is also active in endocrine cancers. Glucocorticosteroids also serve a function in the treatment of several frequently occurring side effects of malignancies as well as general palliative therapy. The corticosteroids are also powerful immunosuppressants, that are used to prevent organ transplant rejection, and in high dose to treat rejection episodes. Corticosteroids may cause osteoporosis, iatrogenic Cushing's syndrome, suppress response to infection and allow diseases such as septicemia or tuberculosis to reach an advanced stage before being recognized *(see also section 5.3; 9.1.2; 10.3&12.3)*

Ciclosporin (cyclosporin) is a calcineurin inhibitor, a powerful immunosuppressant that is non-myelotoxic but nephrotoxic. It has relatively selective effects on T lymphocytes. It can be given orally or by IV infusion. Ciclosporin has revolutionized the field of organ and tissue transplantation, significantly reducing the morbidity and the incidence of rejection. It is particularly useful for the prevention of graft rejection following bone marrow and kidney transplantation and for prophylaxis and treatment of graft- versus-host disease. Its most serious toxic effect is on the kidney which is resulted in increased concentration of blood urea and creatinine. Hypertension is not so very uncommon.

Tacrolimus is also a calcineurin inhibitor. Although chemically not related to ciclosporin it has a similar mode of action and side effects with a greater incidence of neurotoxicity and nephrotoxicity. In some cases cardiomyopathy is also common. Disturbances of glucose metabolism also appear to be significant; hypertrichosis appear to be less of a problem than with ciclosporin.

Basiliximab and **daclizumab** are monoclonal antibodies that prevent T lymphocytes proliferation; they have recently been introduced for prophylaxis of acute rejection in allergic renal transplantation. They are given with ciclosporin and corticosteroid immunosuppressant regimens; their use should be confined to specialist centers.

BASILIXIMAB

Indications: *see notes above*
Side-effects: severe hypersensitivity reactions and cytokine release syndrome have been reported. *see section 14.1*
Cautions: breast feeding and pregnancy *(*contraception during treatment and up to 16 weeks after last dose)
Contraindications: known hypersensitivity to basiliximab or any other component of the formulation
Dose: by intravenous injection or by intravenous infusion,20mg within 2 hours before transplant surgery and20mg 4 days after surgery; withhold second dose ifsevere hypersensitivity or graft loss occurs; CHILD and ADOLESCENT 1–17 years, body-weight under 35 kg,10mg within 2 hours before transplant surgery and10mg 4 days after surgery; body-weight over 35 kg,adult dose

Proprietary Preparation
Simulect[I] *(Novartis),* Inj.,(I.V infusion) 20 mg/vial, Tk.102884.00/Vial

CICLOSPORIN

Indications: as the notes above and under atopic dermatitis, psoriasis and rheumatoid arthritis
Cautions: monitoring of kidney function is very important. Dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction in transplant patients or discontinuation in non-transplant patients; liver functions to be monitored based on serum bilirubin and liver enzymes; monitor blood pressure; discontinue if hypertension develops. Monitor serum potassium especially in marked renal impairment; pregnancy

and breast feeding. One has to keep in mind about Nephrotic syndrome, atopic dermatitis, psoriasis and rheumatoid arthritis.
Note: contains polyethoxylated castor oil which has been associated with anaphylaxis- observe for at least 30 minutes after starting infusion and at frequent intervals thereafter
Contraindications: uncontrolled hypertension or infections
Interactions: *see Appendix-2*
Side-effects: commonly dose dependent increase in serum creatinine and urea during first few weeks and less commonly renal structural changes on long term administration; oedema, pancreatitis, neuropathy, confusion, paresthesia, convulsions, amenorrhea; muscle weakness, cramps, myopathy, gynaeco-mastia; thrombocytopenia, haemolytic uraemic syndrome; hypertrichosis, tremor, hypertension (specially in heart transplant patients) hepatic dysfunction, fatigue, gingival hypertrophy, gastrointestinal disturbances, and burning sensation in hands and feet, hyperkalaemia, hyperuricaemia, hypomagnesaemia
Dose: organ transplantation, used alone, 10-15 mg/kg by mouth before 4-12 transplantation followed by 10-15 mg/kg daily for 1-2 weeks postoperatively then reduced to 2-6 mg/kg daily for maintenance (dose should be adjusted by monitoring blood concentrations and renal function); dose to be lower if given concomitantly with other immunosuppressant; if necessary one third oral dose can be given by intravenous infusion over 2-6 hours
Bone marrow transplantation, prevention and treatment of graft-versus-host disease, 3-5 mg/kg daily by intravenous infusion over 2-6 hours from day before transplantation to 2 weeks post operatively (12.5-15 mg/kg daily by mouth) then 12.5 mg/kg daily by mouth for 3-6 months then tailed off (may take up to a year after transplantation)
Nephrotic syndrome, by mouth, 5 mg/kg daily in 2 divided doses; CHILD 6 mg/kg daily in 2 divided dose according to proteinuria and serum creatinine measurements; discontinue after 3 months if no improvement in glomerulonephritis or glumerulosclerosis (after 6 months in membranous glomerulonephritis)

Proprietary Preparations
Imural *(Techno),* Cap., 100 mg, Tk. 60.00/Cap.
Sandimmun Neoral[I] *(R.P. Scherer)* Cap., 25 mg, , Tk. 59.00/Cap.; 50 mg, Tk. 117.00/Cap.; 100 mg, Tk. 234.00/Cap.
Sporium *(Incepta),* Solu, 10 gm/100 ml, Tk. 2,385/10 gm

TACROLIMUS

Indications: used to prevent body from rejecting a heart, liver, or kidney transplant. It may be used along with other medicines and see also notes above
Cautions: *see section 14.1 and notes above*; monitor blood pressure, ECG, fasting blood-glucose concentration
Interactions: *see Appendix-2*
Contraindications: pregnancy breast-feeding; hypersensitivity to macrolides; avoid concurrent administration with ciclosporin
Side-effects: *see section14.1 and notes above*
Dose: *consult product literature*

Proprietary Preparation
Tacrolimus Sandoz *(Sandoz),* Cap., 1 mg, Tk. 42.82/Cap.; 5 mg, Tk. 174.80/Cap.

14.2.3 RITUXIMAB

Rituximab is a monoclonal antibody that has recently been introduced for the treatment of chemotherapy of resistant advanced follicular lymphoma. It causes lysis of B lymphocytes. Rituximab should be given very carefully in patients with a history of angina, arrhythmia and heart failure. Full resuscitation facilities should be ready as with other cytotoxic drugs. Side-effects include rash, pruritus, fever and chills, nausea and vomiting, angioedema, bronchospasm and dyspnoea

An analgesic and antihistamine to be given to the patients before each dose of Rituximab as prophylactic.

RITUXIMAB

Indications: chemotherapy resistant advanced follicular lymphoma.
Cautions: *see notes above but for full details consult product literature;* pregnancy
Contraindications: pregnancy and breast-feeding
Side-effects: *see notes above*
Dose: 375 mg/m2 administered for once weekly for 4 weeks (at day 01, day 08, day 15, and day 22). In diffuse NHL it should be administer along CHOP at day 1 of each chemotherapy.

Proprietary Preparations
Mabthera[I] *(Roche),* Inj. 500 mg/50 ml, Tk.135,406.30/Vial; 100mg/10 ml,Tk. 27,081.13/Vial
Rituxim*(Beacon),* Inj., 100 mg, Tk. 13,000.00/Vial ; 500 mg, Tk. 60,000.00/Vial

14.2.4 INTERFERONS

The **interferons** are a family of proteins that are produced by cells in response to viral infections or stimulation with double stranded RNA, antigens or mitogens. They may be produced through recombinant DNA technology. The interferons can interfere with subsequent viral challenge, and they have many immunomodulating and antiproliferative effects.
Interferon Alfa: is derived from leucocytes, macrophages and through recombinant DNA technology. Interferon alfa preparations are also used in the treatment of chronic hepatitis B and chronic hepatitis C, certain lymphomas and solid tumors. The symptoms of side-effects are dose related which include nausea, influenza like symptoms, lethargy, myalgia, hypotension and arrhythmia. Severe bronchospasm, nephrotoxicity and hepatotoxicity have been reported.

INTERFERON ALFA

Indications: AIDS related Kaposis sarcoma, hairy cell leukemia, follicular lymphoma, chronic myelogenous leukemia, lymph or liver metastasis of carcinoid tumor, chronic hepatitis B, chronic hepatitis C, adjunct to surgery in malignant melanoma and maintenance of remission in multiple myeloma; *see also the notes above*
Cautions: consult product literature
Interactions: *see also Appendix-2.*
Contraindications: *consult product literature.*
Side-effects: *see notes above*
Dose : for chronic hepatitis B: Interferon alfa-2a is given in a dose of 2.5 to 5 million units/m^2 body surface 3 times a week by SC injection for 4 to 6 months;
For chronic hepatitis C: Interferon alfa-2a is given in a dose of 3 to 6 million units/m^2 body surface 3 times a week for 4 to 6 months followed by 3 million units 3 times a week for an additional 6 months

Proprietary Preparation
Roferon-A[I] *(Roche),* Inj., 3 MIU, Tk. 2,391.53/Vial; 4.5 MIU, Tk. 3,531.70/Vial

PEG INTERFERON ALFA

Indications: combine with ribavirin for chronic hepatitis C; as monotherapy if ribavirin not tolerated or contra-indicated
Interactions: *see Appendix-2*
Side-effects: *see notes above*
Dose: *Consult with oncologist*

Proprietary Preparations
Pegasys [I] *(Roche),* Inj. 180 mcg/ml, Tk. Tk. 25,051.25/Vial; 135 mcg/ml, Tk. Tk. 22,576.23/Vial
Peg Intron[I] *(Schering),* Powder and Solvent for solution for inj., 80 mcg/vial, Tk. 12698.94/0.5 ml Vial
Optipeg-A*(Incepta),* Inj.,(P.F Syringe), 180 mg/ Syringe , Tk. 9,800.00/Syringe ;135 mg/Prefilled Syringe , Tk. 8,800.00/Prefilled Syringe

Pegin *(Beacon),* Inj., 135 mg/ Syringe, Tk. 8,800.00/Prefilled Syringe ;180 mg/ Syringe, Tk. 9,800.00/ Syringe

14.2.5 ALDESLEUKIN

Aldesleukin is a preparation of recombinant interleukin-2 has had some action on metastatic renal cell carcinoma unresponsive to other therapy at the expense of profound toxic effects due to vascular leakage causing pulmonary oedema and hypotension. Bone marrow, hepatic, renal, thyroid and CNS toxicity are also severe.

14.2.6 BCG IMMUNOTHERAPEUTICS

The drug promotes local acute inflammatory and subacute granulomatous reactions with histiocytic and leucocytic infiltration in the epithelium of the urinary bladder. The local inflammatory effects are associated with an elimination or reduction of superficial cancerous lesions of the urinary bladder. The anti-tumour effect appears to be T-lymphocytes dependent.

BCG IMMUNOTHERAPEUTICS

Indications: for the treatment of superficial transient cell carcinoma of the urinary bladder; for intravesical use in the treatment and prophylaxis of primary or recurrent carcinoma *in situ* of the urinary bladder
Cautions: pregnancy, lactation, pneumonitis, hepatitis, and other organ dysfunction outside of gastrointestinal tract with granulomatous inflammation on biopsy, respiratory distress
Contraindications: receiving immunosuppressive therapy (with drugs or radiation) or with compromised immune systems because of the danger of a systemic BCG reaction, pyrexia of unknown origin, urinary tract infection caused by bacteria
Interactions: drug combination containing bone marrow depressants and or immunosuppressants and or radiation may impair the response of the drug
Side-effects: most common local reactions are transient dysuria and urinary frequency, transient fever, skin rash, arthralgia, or migratory arthritis, systemic BCG reactions
Dose: induction treatment comprises 6 weekly intravesical treatment with BCG Immunotherapeutic, each treatment dose comprises 3 vials of the BCG Immunotherapeutic. After a 6 weeks pause, another dose of 3 vials of the BCG Immunotherapeutic should be given intravesically once weekly for 1-3 weeks. 3 weekly doses should definitely be given to patients who still have evidence of bladder cancer.

14.3. SEX HORMONES AND HORMONE ANTAGONISTS IN MALIGNANT DISEASES.

Tumours derived from hormone-sensitive tissues may be hormone-dependent. Their growth can be inhibited by hormones, with opposing actions, by hormone antagonists or by agents that inhibit the synthesis of relevant hormones. Hormones and hormone analogues have inhibitory actions on particular tissue and can play an important role in the treatment of breast, prostate, and endometrial cancer. The objective of the hormone therapy is to provide excellent relief of symptoms for a period of years. Response to the treatment and toxicity to be carefully monitored and treatment to be changed if progression occurs or side-effects exceed benefit.

14.3.1 ESTROGENS

Diethylstillbestrol (stillbestrol), a synthetic non-steroidal estrogen has been used in the palliation of prostate and breast cancer. Dose related side-

effects include nausea, fluid retention and arterial and venous thrombosis. Impotence and gynecomastia occur in men and withdrawal bleeding may occur in women. Hypercalcaemia and bone pain may also occur in breast cancer. Stillbestrol should be used with caution in cardiovascular disease, hepatic and renal impairment; it is contraindicated in pregnancy.

Fosfestrol a non-steroidal estrogen has become activated to stillbestrol and is used for prostate cancer. Side-effects are as for diethylstilbestrol; in addition, perineal pain may complicate intravenous use.

Ethynylestradiol is the most potent estrogen available; unlike other estrogens it is slowly metabolized in the liver. It is used in breast cancer.

FOSFESTROL TETRA SODIUM

Indication: prostrate cancer
Caution: *see under diethylstilbestrol and notes above*
Side-effects: also nausea and vomiting: after intravenous injection peritoneal irritation and pain on bony metastasis
Dose: *by slow intravenous injection,* 0.6-1.2 g daily for at least 5 days; maintenance, initially up to 240 mg 3 times daily for 7 days then reducing over 14 days to 120-360 mg daily in divided doses

Proprietary Preparation
Honvan (I) *(Astamedica)* Tab. 50mg, Tk.20.82/Tab.Inj. 60 mg/ml.

14.3.2 PROGESTOGENS

Progestogens are largely used as second or third line therapy in breast cancer. They are also used to treat endometrial cancer and renal cell carcinoma, but are little used for prostate cancer. **Medroxyprogesterone** or **megestrol** are usually chosen and can be given orally, high-dose or parenteral treatment cannot be recommended. Side-effects are mild but may include nausea, fluid retention and weight gain.

MEDROXYPROGESTERONE ACETATE

Indications: *see notes above*
Cautions: diabetes, hypertension, cardiac or renal disease
Contraindications: pregnancy, undiagnosed vaginal bleeding, hepatic impairment or active liver disease, severe arterial disease, breast and genital tract cancer
Side-effects: acne, urticaria, fluid retention, weight changes, gastrointestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles; also depressions, insomnia, somnolence, alopecia, hirsutism, anaphylactoid reactions
Dose: *by mouth,* endometrial, prostrate and renal cancer, 100-500 mg daily; breast cancer, various doses in range 0.4-1.5 g daily
By deep intramuscular injection into gluteal muscle, various doses in range 1 g daily down to 250 g weekly

Proprietary Preparations
see section: 5.4.2.2

NORETHISTERONE

Indication: *see notes above*
Cautions: *see under medroxyprogesterone acetate*
Contraindications: *see under medroxyprogesterone acetate*
Side-effects: *see under medroxyprogesterone acetate*; more virilizing and greater incidence of liver disturbances and jaundice; exacerbation of epilepsy and migraine
Dose: breast cancer, 40 mg daily, increased to 60 mg daily if required

Proprietary Preparations
see section: 5.4.2.2

14.3.3 ANDROGENS

Testesterone esters are occasionally still used as second or third line therapy for metastatic breast cancer.

14.3.4 HORMONE ANTAGONISTS

14.3.4.1 BREAST CANCER

The management of patients with breast cancer involves surgery, radiotherapy, drug therapy, or a combination of these. All women with invasive breast cancer should be considered for the adjuvant therapy, which is determined by assessment of risk of recurrence, estrogen receptor status of primary tumor and menopausal status.

Tamoxifen is an estrogen antagonist with actions similar to clomiphene. It is given in the adjuvant endocrine therapy of early breast cancer and is also given for the palliative treatment of advanced disease. Tamoxifen is generally well tolerated and the most frequent adverse effects are hot flushes, nausea and vomiting. Other adverse effects include edema, vaginal bleeding, pruritus, increased tendency to thromboembolism. Treatment with tamoxifen delays the growth of metastases and increases survival; if tolerated it should be continued for at least 5 years.

Toremifene, is an antiestrogen which has properties similar to tamoxifen is used for hormone dependent metastatic breast cancer in post-menopausal patients. It is given by mouth, 60 mg daily.

Aminoglutethimide act predominantly by blocking the conversion of androgen to estrogens in the peripheral tissues. Aminoglutethimide is used as second line treatment for prostate cancer. Toxicity may include drowsiness, drug fever, and morbiliform eruption; these side-effects are generally reversible. It causes induction of hepatic enzymes and may require modification of doses of other drugs.

Anastrozole and **Letrozole** are inhibitors of aromatase system used in the treatment of breast cancer. Recently introduced **Formestane** and **exemestane,** steroidal aromatase inhibitors are used to treat advanced postmenopausal breast cancer. They are more tolerated than aminoglutethimide and corticosteroid replacement therapy.

Trilostane is also used for post-menopausal breast cancer. It is well tolerated. Diarrhea and abdominal discomfort are their main side effects. It may cause adrenal hypofunction and need corticosteroid replacement therapy.

Goserelin, a good gonadorelin analogue is also indicated for advanced breast cancer in post-menopausal women.

ANASTROZOLE

Indications: early breast cancer in postmenopausal women as adjuvant treatment (treatment following surgery with or without radiation), first-line treatment for hormone receptor-positive or hormone receptor unknown, locally advanced or metastatic breast cancer in postmenopausal women.
Cautions: renal and hepatic impairment
Contraindications: pregnancy and breast-feeding, not for premenopausal women
Side-effects: arthralgia, arthritis, bone fractures, bone pain, rash (including Stevens-Johnson syndrome)
Dose: 1 mg tablet taken once a day and consult product literature

Proprietary Preparation
Anastrol *(Beacon),* Tab.,1mg, Tk.500/Tab.

EXEMESTANE

Indication: to treat breast cancer in postmenopausal women. It is often given to women whose cancer has progressed even after taking tamoxifen therapy for 2 to 3 year, *See notes above*
Cautions: renal and hepatic impairment
Interactions: *see Appendix-2*
Contraindications: pregnancy and breast-feeding
Side-effects: *see notes above*
Dose: 25 mg daily

Generic Preparation
Tablet 25mg

LETROZOLE

Indications: advanced breast cancer in post-menopausal women in whom anti-estrogen therapy has failed
Caution: severe renal impairment
Contraindications: severe hepatic impairment, pre-menopausal women
Side-effects: hot flushes, gastrointestinal disturbances, chest pain, cough, dizziness, fatigue, headache, infection, musculoskeletal pain, peripheral edema, rash, pruritus
Dose: 2.5 mg daily until tumor progression is evident

Proprietary Preparations
Endofree *(Incepta),* Tab. , 2.5 mg, Tk. 40.00/Tab.
Femara[I] *(Novartis).* Tab. 2.5 mg, Tk. 375.00/Tab.
Femzole *(Beximco),* Tab. 2.5 mg, Tk. 40.00/Tab.
Lenor *(Eskayef),* Tab. 2.5 mg, Tk. 40.00/Tab.
Lerozol *(Square),* Tab. 2.5 mg, Tk. 40.15/Tab.
Letrol *(Renata),* Tab. 2.5 mg, Tk. 40.15/Tab.
Lexel *(Beacon),* Tab. 2.5 mg, Tk. 40.00/Tab.
Loreta*(Popular),* Tab. 2.5 mg, Tk. 40.00/Tab.

TAMOXIFEN[ED]

Indications: *see notes above*
Caution: increased risk of thromboembolic events when used with cytotoxics, cystic ovarian swelling, pre-menopausal women, hypercalcaemia in bony metastasis
Contraindications: pregnancy and breast-feeding
Interactions: *see Appendix-2*
Side-effects: hot flushes, vaginal bleeding or suppression of menstruation in some premenopausal women, vaginal discharges, pruritus vulvae, gastro-intestinal disturbances, headache, alopecia, rashes, uterine fibroids; visual disturbances, leucopenia, sometimes anemia and thrombocytopenia
Dose: breast cancer, 20 mg daily for at least 5 years
Anovulatory fertility, 20 mg on day 2, 3, 4 and 5 of cycles; if necessary the daily dose may be increased to 40 mg then 80 mg for subsequent courses; if cycles irregular, start initial course on any day, with subsequent course starting 45 days later or on day 2 of cycle if menstruation occurs

Proprietary Preparations
G-Tamoxifen *(Gonoshasthaya),* Tab., 10 mg, TK.6.00/Tab.; 20 mg, Tk.10.00/Tab.
Tamolex *(Beacon),* Tab., 10 mg, Tk. 8.00/Tab.; 20 mg, Tk. 16.00/Tab.
Tamona *(Beximco),* Tab., 10 mg, Tk. 10.07/Tab.; 20 mg, Tk. 16.07/Tab.
Tamoxen *(General),* Tab., 10 mg, Tk. 10.04/Tab.; 20 mg, Tk. 16.06/Tab.

14.3.4.2 PROSTATE CANCER AND GONADORELIN ANALOGUES

Hormonal treatment in metastatic cancer of the prostate is aimed to deplete androgen. Analogues of gonadotropin-releasing hormones, such as **buserlin, goserelin, leuprorelin** or **triptorelin** can under certain circumstances be made use of advanced prostate cancer and in some cases of advanced breast cancer in pre-menopausal women.
The standard treatment is bilateral sub-capsular orchidectomy, which commonly results in response lasting 12-18 months. Alternatively, a gonadorelin analogue may be given.
Gonadorelin analogues are expensive and require parenteral administration. Initially these analogues stimulate then depress lutenising hormone released by pituitary. During the first 2 weeks of treatment there is surge of testosterone secretion associated with progression with prostate cancer. In susceptible patients this tumor progression may cause spinal cord compression, ureteric obstruction or increased bone pain. When such problems are anticipated, orchiectomy or concomitant use of an anti-androgen such as cyproterone acetate or flutamide are suggested; anti androgen treatment to be started 3 days before the gonadorelin analogues and to be continued for 3 weeks.
Cautions: Men at risk of tumor flare should be monitored closely during the metabolic bone disease in women; the injection site should be rotated.

Side-effects: hot flushes, sweating, sexual dysfunction, vaginal dryness or bleeding, and gynecomastia or changes in breast size. Sign and symptoms of prostate and breast cancer may worsen initially. Other side-effects include hypersensitivity reactions injection site reactions, headache, visual disturbances, dizziness, arthralgia, gastrointestinal disturbances, weight changes, sleep disorders.

ANTI-ANDROGENS: **Cyproterone acetate, flutamide,** and **bicalutamide** are anti-androgens which can be used to cover the tumor flare which may occur after commencing gonadorelin analogue administration. **Cyproterone acetate** and **flutamide** are also used alone in patients with metastatic prostate cancer refractory to gonadorelin analogue therapy. Bicalutamide is used alone in patients with locally advanced, metastatic prostate cancer.

Abiraterone: It is used in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel

ABIRATERONE ACETATE

Indications: *see notes above*
Cautions: cardiovascular disease; control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid hepatic impairment retention at least monthly; diabetes; hepatic impairment; renal impairment
Interaction: *see appendix-2*
Side-effects: *see notes above*
Dose: 1 g once daily
Note: Consult product literature for dose of concurrent prednisone or prednisolone

Proprietary Preparation
Zytix *(Beacon)*, Tab., 250mg, Tk.26.67/Tab.

FLUTAMIDE

Indication: advanced prostate cancer
Cautions: cardiac disease, hepatic impairment, abdominal pain, unexplained influenza-like syndromes
Interactions: *see appendix-2*
Side-effects: *see notes above*
Dose: 250 mg 3 times daily

Proprietary Preparation
Proscan *(Renata),* Tab., 250 mg, Tk. 12/Tab.

14.3.4.3 SOMATOSTATIN ANALOGUES

Oxtreotide and **lanreotide,** the recently introduced analogues of somatostatin, hypothalamic release inhibiting hormone. They are indicated for relief of symptoms carcinoid tumors and acromegaly.