**Vinorelbine**

Vinca alkaloid (synthetic)
Mitotic inhibitor/ anti-microtubule agent
Cell cycle specific (acts in M phase)

*Mechanism of action:*
It inhibits polymerization of tubulin and thereby prevents microtubule assembly during mitosis. It thus causes cell cycle arrest, leading to cell death.

*Pharmacokinetics:* Oral absorption variable. Well absorbed after IV administration. Widely distributed. Metabolised in liver by CYP450 system. Excreted mainly in feces.

*Route of administration:* Diluted to a concentration of 1.5-3 mg/ml in NS/5%D over 6-10 minutes via free-flowing IV line or as infusion.

*Special precautions:* (1) Should not be used in patients with liver dysfunction-dose reduction is required.

(2) As it is a vesicant, so should be given only via free-flowing IV line. If extravasation occurs, elevation of limb, ice pack, etc should be administered.
(3) Used with CDDP, there is increased chance of BM suppression.
(4) Used with MMC, there is increased chance of acute allergic reactions.
(5) Should be used with caution in patients on medications which are inhibitors of the CYP450 system.

*Toxicities:*
(1) BM depression, esp neutropenia (dose-limiting)
(2) Nausea & vomiting (moderate)
(3) Constipation, diarrhea, stomatitis, anorexia
(4) Neurotoxicity (mild)
(5) Hypersensitivity
(6) Alopecia
(7) Fatigue
(8) Vesicant (if extravasated)
(9) SIADH

*Dose:* 30 $mg/m^2$ IV weekly

*Indications:*
(1) NSCLC
(2) Ca Breast ($2^{nd}/3^{rd}$ line
(3) Ca Ovary ($2^{nd}$ line)

# Vinblastine

Vinca alkaloid (synthetic)
Mitotic inhibitor/ anti-microtubule agent
Cell cycle specific (acts in M phase)

*Mechanism of action:*
It inhibits polymerization of tubulin and thereby prevents microtubule assembly during mitosis. It thus causes cell cycle arrest, leading to cell death.

*Pharmacokinetics:* Oral absorption poor. Well absorbed after IV administration. Widely distributed. Metabolised in liver by CYP450 system. Excreted mainly in feces.

*Route of administration:* Given as IV bolus after dilution in NS/5%D

*Special precautions:* (1) Should not be used in patients with liver dysfunction-dose reduction is required.

(2) As it is a vesicant, so should be given only via free-flowing IV line. If extravasation occurs, elevation of limb, ice pack, etc should be administered.
(3) Used with Bleomycin, there is increased chance of Raynaud's phenomenon.
(4) Should be used with caution in patients on medications which are inhibitors of the CYP450 system.

*Toxicities:*
(1) BM depression, esp neutropenia (dose-limiting)
(2) Nausea & vomiting (moderate)
(3) Constipation, diarrhea, stomatitis, anorexia
(4) Neurotoxicity (mild)
(5) Hypersensitivity
(6) Alopecia
(7) Vesicant (if extravasated)
(8) SIADH
(9) Hypertension, stroke, AMI

*Dose:* 6 mg/$m^2$ IV D1, D15 q D28 (ABVD)

*Indications:*
(1) HD (ABVD regime)
(2) Germ cell tumors (PVB, VeIP)

# Vincristine

Vinca alkaloid (natural)
Mitotic inhibitor/ anti-microtubule agent
Cell cycle specific (acts in M phase)

*Mechanism of action:*
It inhibits polymerization of tubulin and thereby prevents microtubule assembly during mitosis. It thus causes cell cycle arrest, leading to cell death.

*Pharmacokinetics:* Oral absorption poor. Well absorbed after IV administration. Widely distributed. Metabolised in liver by CYP450 system. Excreted mainly in feces.

*Route of administration:* Given as IV bolus over 1 minute, after dilution in NS/5%D, through free-flowing IV line.

*Special precautions:* (1) Should not be used in patients with liver dysfunction-dose reduction is required.

(2) As it is a vesicant, so should be given only via free-flowing IV line. If extravasation occurs, elevation of limb, ice pack, etc should be administered.
(3) Used with CDDP or Taxanes, there is increased chance of severe neurotoxicity
(4) Should be used with caution in patients on medications which are inhibitors of the CYP450 system.
(5) Fatal if administred intra-thecally.
(6) As constipation is very common, patients should be warned and advised to take laxatives.
(7) VCR clearance is inhibited by L-Asparaginase.
(8) VCR increases MTX uptake into cells.
(9) A baseline neurological status should be determined before first administration. If severe neurotoxicity occurs, VCR should be stopped.

*Toxicities:*

(1) Neurotoxicity (Dose limiting). Commonest toxicity. Includes peripheral neuropathy (reduced deep tendon reflexes, paresthesias, paralysis) as well as autonomic neuropathy (constipation, ileus, orthostatic hypotension) as well as cranial neuropathy, ataxia and coma. Fatal if administered intrathecally.
(2) Constipation, abdominal pain, ileus
(3) Bone marrow depression (mild)
(4) Hypersensitivity
(5) Alopecia
(6) Vesicant (if extravasated)
(7) SIADH
(8) Sterility

*Dose:* 0.5-1.5 mg/$m^2$ IV weekly (mmaximum single dose=2mg)

*Indications:*

(1) HD (MOPP, COPP)
(2) NHL (CHOP)
(3) Soft Tissue Sarcoma
(4) Pediatric tumors (Retinoblastoma, Neuroblastoma, Wilms' tumor)
(5) ALL
(6) Gestational Trophoblastic Neoplasia (EMA-CO)

## Paclitaxel

Vinca alkaloid (natural)
Mitotic inhibitor/ anti-microtubule agent
Cell cycle specific (acts in M phase)

*Mechanism of action:*
It promotes polymerization of tubulin and prevents dynamic microtubule assembly during mitosis. It thus causes cell cycle arrest, leading to cell death.

*Pharmacokinetics:* Oral absorption poor. Well absorbed after IV administration. Widely distributed. Metabolised in liver by CYP450 system. Excreted mainly in feces.

*Route of administration:* Given as IV infusion, diluted in Cremaphor EL which is further diluted in NS/5%D to give a final drug concentration of 0.3-1.2 mg/ml.

*Special precautions:* (1) Should not be used in patients with liver dysfunction-dose reduction is required.

(2) Used with CDDP or in patients with pre-existing neuropathy (eg DM), there is increased chance of severe neurotoxicity
(3) Should be used with caution in patients on medications which are inhibitors of the CYP450 system.
(4) Potent radiosensitiser.
(5) Hypersensitivity to the diluent Cremaphor 80 is quite common and occurs in about 20-40% cases, usually within 2-3 minutes, and always within 10 minutes. The incidence of hypersensitivity is the same irrespective of whether the drug is given as 3-hour or 24-hour infusion The patient should be premedicated with 20 mg Dexamethasone 12 hours and 6 hours before administration, as also with Diphenhydramine 50 mg IV and Ranitidine 50 mg IV 30 minutes before drug administration. The patient's vital signs should be monitored carefully during the first hour of infusion. Full resuscitation facilities should be available. If

moderate to severe hypersensitivity occurs, infusion should be stopped and patient should be treated with Dexamethasone 20 mg IV 6 hourly and Diphenhydramine 50 mg IV.

(6) Should not be given in PVC bags or infusion sets, as it causes leaching of the diluent Cremaphor 80.
(7) When used in combination with CDDP or Carboplatin, the platinum agent should be given first, as they inhibit excretion of Paclitaxel and therefore potentiate its effect.
(8) When used in combination with Doxorubicin, the anthracycline should be given first as Paclitaxel retards its excetion leading to increased toxicity (myelosuppresion)
(9) Should not be given in patients with known previous heart disease.

*Toxicities:*

(1) Bone marrow depression (dose-limiting)
(2) Hypersensitivity (skin rash/ erythema ,flushing, hypotension, bronchospasm, dyspnoea)
(3) Neurotoxicity (peripheral sensory neuropathy). The incidence is higher with longer infusion times and with higher doses.
(4) Nausea, vomiting, diarrhea (30-40%)-mild to moderate.
(5) Alopecia (100%)
(6) Transient asymptomatic bradycardia (30%) Rarely other more serious conduction problems.

*Dose:* 175 mg/$m^2$ IV as 3-hour infusion q 3-weeks (commonest regime)

*Indications:*

(1) Ca Breast (node-positive)
(2) Ca Ovary ($1^{st}$ line)
(3) Ca H&N
(4) Ca Oesophagus
(5) NSCLC ($1^{st}$ line)

## Docetaxel

Vinca alkaloid (natural)
Mitotic inhibitor/ anti-microtubule agent
Cell cycle specific (acts in M phase)

*Mechanism of action:*
It promotes polymerization of tubulin and prevents dynamic microtubule assembly during mitosis. It thus causes cell cycle arrest, leading to cell death.

*Pharmacokinetics:* Oral absorption poor. Well absorbed after IV administration. Widely distributed. Metabolised in liver by CYP450 system. Excreted mainly in feces.

*Route of administration:* Given as IV infusion, diluted in Polysorbate 80 which is further diluted in NS/5%D to give a final drug concentration of 0.3-0.94 mg/ml.

*Special precautions:* (1) Should not be used in patients with liver dysfunction-dose reduction is required.

(2) Should be used with caution in patients on medications which are inhibitors of the CYP450 system.
(3) Potent radiosensitiser.
(4) Hypersensitivity to the diluent Polysorbate 80 is quite common and occurs in about 20-40% cases, usually within 2-3 minutes, and always within 10 minutes. The patient should be premedicated with Dexamethasone 8 mg PO BD 3 days starting on the day before drug administration. The patient's vital signs should be monitored carefully during the first hour of infusion. Full resuscitation facilities should be available. If moderate to severe hypersensitivity occurs, infusion should be stopped and patient should be treated with Dexamethasone 20 mg IV 6 hourly and Diphenhydramine 50 mg IV.
(5) Should not be given in PVC bags or infusion sets, as it causes leaching of the diluent Cremaphor 80.
(6) When used in combination with CDDP or Carboplatin, the platinum agent should be given first, as they inhibit excretion of Docetaxel and therefore potentiate its effect.
(7) When used in combination with Doxorubicin, the anthracycline should be given first as Docetaxel retards its excetion leading to increased toxicity (myelosuppresion)
(8) Should not be given in patients with known previous heart disease.

*Toxicities:*

(1) Bone marrow depression (dose-limiting)
(2) Hypersensitivity (skin rash/ erythema ,flushing, hypotension, bronchospasm, dyspnoea)
(3) Neurotoxicity (peripheral sensory neuropathy). Milder than with Paclitaxel.
(4) Nausea, vomiting, diarrhea (30-40%)-mild to moderate.
(5) Alopecia (100%)
(6) Fluid retention syndrome (50%)-manifests as weight gain, pleural effusion, oedema and ascites. The incidence is reduced by steroid premedication.
(7) Rash
(8) Fever
(9) Vesicant
(10) Generalised fatigue and asthenia

*Dose:* 60-100 mg/m$^2$ IV as 1-hour infusion q 3-weeks (commonest regime)

*Indications:*

(1) Ca Breast ($2^{nd}$ line)
(2) Ca Ovary ($2^{nd}$ line)
(3) NSCLC ($1^{st}$/ $2^{nd}$ line)
(4) Ca. Prostate (hormone-refractory metastatic disease only)

## Nitrosoureas

Alkylating agent
Cell-cycle non-specific

*Mechanism of action:* DNA strand cross-linking leading to apoptosis.
*Route of administration:* BCNU (Carmustine) by IV injection or as wafer (Gliadel)
CCNU (Lomustine) by PO route
*Pharmacokinetics:* CCNU is well-absorbed by oral route while BCNU is given only by IV route. Well-distibuted, attain therapeutic concentrations in CNS. Metabolised in liver by CYP450 system. Excreted via kidneys.

*Toxicities:*

(1) Bone marrow depression (dose-limiting, affects all cell types, cumulative, nadir at 4-6 weeks)
(2) Sterility & impotence in male; menopause & infertility in female
(3) Interstitial lung disease (at high doses)
(4) Intense burning pain on injection (BCNU)
(5) Nausea & vomiting (severe)
(6) Nephrotoxicity
(7) Neurotoxicity (dysarthria, ataxia, confusion, lethargy)
(8) Induction of $2^{nd}$ malignancy-AML, MDS

*Dose:* BCNU =200 mg/$m^2$ IV (1-2 hour infusion) every 6 weeks
CCNU=130 mg/$m^2$ PO every 6 weeks

*Indications:*

(1) Brain tumors
(2) HD
(3) NHL

## Cisplatin

Cis-diamminedichloroplatinum
Platinum agent (atypical alkylating agent)
Cell-cycle non-specific

*Mechanism of action:* Forms covalent adducts with DNA, (binds to DNA at at least 2sites producing both inter- and intra- strand cross-linking) retards DNA synthesis and function.

*Pharmacokinetics:* Well absorbed after parenteral administration. Widely distributed. Metabolised in liver. Excreted by kidneys-complete excretion is delayed upto 3-5 days.

*Indications:*

(1) NSCLC (1st line)
(2) SCLC (1st line)
(3) Epithelial Ca. Ovary (1st line)
(4) Germ Cell Tumors (1st line)
(5) Ca. Urinary Bladder (1st line)
(6) Ca. oesophagus
(7) Ca. H & N
(8) Ca. Anal Canal

*Dose:* 20 mg/$m^2$/ day IV D1-D5 (BEP regime for germ cell tumors)
75 mg/$m^2$ IV every 3 weeks (most other regimes)
40 mg/m IV weekly (radiosensitiser)

*Special considerations:*

(1) In order to prevent nephrotoxicity, prehydration and diuresis are required during administration. Hydration is done by 1 liter of fluid (NS with extra 20 Meq of KCl) before and after the drug. Diuresis is done by Mannitol infusion and/or Frusemide injection. Urine output should be > 100 cc/hour.
(2) CDDP is contraindicated in patients with severe renal dysfunction. In cases with mild renal dysfunction, dose reduction is necessary. It should not be used together with other nephrotoxic drugs. Renal function should be monitored during treatment.
(3) Used with Paclitaxel, there is greater chance of severe peripheral neuropathy.
(4) Should not be used together with other ototoxic drugs
(5) Potent radiosensitiser.
(6) Retards the elimination of Bleomycin, Ifosfamide, MTX, Etoposide and Paclitaxel-potentiates their action as well as increases toxicity.

*Toxicities:*

(1) Nephrotoxicity-dose limiting. Occurs in 30-40% patients. Acute Tubular Necrosis is the typical lesion. Manifests around 10-12 days after administration. Reversible. Electrolyte abnormalities are common-hypocalcemia, hypomagnesemia, hypokalemia.
(2) Nausea & vomiting (severe)
(3) Neurotoxicity (peripheral sensory neuropathy)
(4) Ototoxicity
(5) Bone marrow depression
(6) Alopecia
(7) Cardiotoxicity-AMI, vasculitis
(8) Sterility & impotence
(9) Metallic taste
(10) SIADH
(11) Ocular toxicity

(12) Transient elevation of liver enzymes

## Carboplatin

Platinum agent (atypical alkylating agent)
Cell-cycle non-specific

*Mechanism of action:* Forms covalent adducts with DNA, (binds to DNA at at least 2sites producing both inter- and intra- strand cross-linking) retards DNA synthesis and function.
*Pharmacokinetics:* Well absorbed after parenteral administration. Widely distributed. Metabolised in liver. Excreted by kidneys-complete excretion is delayed.

*Indications:*

(1) NSCLC (1st line)
(2) SCLC (1st line)
(3) Epithelial Ca. Ovary (1st line)
(4) Germ Cell Tumors (1st line)
(5) Ca. Urinary Bladder (1st line)

*Dose:* AUC 5-7 mg/ml/min (previously untreated patients)
AUC 4-6 mg/ml/min (previously treated patients)

*Special considerations:*

(1) Carboplatin is contraindicated in patients with severe renal dysfunction. In cases with mild renal dysfunction, dose reduction is necessary. It should not be used together with other nephrotoxic drugs. Renal function should be monitored during treatment.
(2) Routine hydration before administration is not required.
(3) Used with Paclitaxel, there is greater chance of severe peripheral neuropathy.
(4) Potent radiosensitiser.
(5) Dose of Carboplatin is expressed as target AUC. Dose (mg)=Target AUC (mg/ml/min) x [GFR (ml/min) + 25]
(6) Carboplatin exhibits an unique allergic reaction, which develops only after administration of several (>7) courses of the drug.

*Toxicities:*

(1) Bone marrow depression (dose-limiting).
(2) Nephrotoxicity-(less common than CDDP)
(3) Nausea & vomiting (less severe than CDDP)
(4) Neurotoxicity (peripheral sensory neuropathy-less common than CDDP)
(5) Transient elevation of liver enzymes
(6) Allergy
(7) Sterility & impotence

# Oxaliplatin

Diamminocyclolexane platinum
Platinum agent (atypical alkylating agent)
Cell-cycle non-specific

*Mechanism of action:* Forms covalent adducts with DNA, (binds to DNA at at least 2sites producing both inter- and intra- strand cross-linking) retards DNA synthesis and function.
*Pharmacokinetics:* Well absorbed after parenteral administration. Widely distributed. Metabolised in liver. Excreted by kidneys-complete excretion is delayed.

*Indications:*

(1) Metastatic CRC (1$^{st}$ line)
(2) Adjuvant treatment of CRC (1$^{st}$ line)

*Dose:* 85 mg/m$^2$ IV over 2 hours every 2 weeks. Should be diluted in 5%D only.

*Special considerations:*

(1) Should be used with caution in patients with renal dysfunction.
(2) A baseline neurological examination should be done before therapy.

*Toxicities:*

(1) Neurotoxicity (dose-limiting) Reversible, cumulative. Typical toxicity is acute laryngopharyngeal dysasthesia producing dyspnoea/ choking sponataneously/ with exposure to cold, in absence of any obstructive lesion.
(2) Bone marrow depression
(3) Nausea & vomiting
(4) Diarrhoea (80-90% patients receiving Oxaliplatin combinations)
(5) Nephrotoxicity
(6) Allergy