Cell Cycle Specific Agents

Drug	Mechanism of Action	Activation	Pharmcokinetics	Toxicities	Resistance	Notes
Anti-metabolite: Folate analogs						
Methotrexate Rheumatrex®	Inhibition of dihydrofolate reductase, inhibit the generation of tetrahydrofolate and downstream purine and thymine synthesis. Activity is **S-phase** specific	Parent drug and metabolite competitively bind to DHFR	**Well absorbed orally, also administered IV and IT.** 50% plasma protein binding. Excreted principally by the kidney.	**GI disturbances. Myelosuppression** Nephropathy Teratogenic Pulmonary toxicity **High emetogenicity** is dose-related	**1. Impaired cellular uptake** **2. DHFR mutation or gene amplification** **3. Increase MRP drug export**	**Folinic acid rescue allow lethal dose of MTX be used in aggressive chemo-therapy**
Leucovorin (Folinic Acids) Wellcovorin ®	1. protection of normal cells in high dose MTX therapy 2. synergistic with 5-FU to increase formation of TS-5dUMP-MTHR ternary complex.	Rapidly converted into 5-methyltetrahydrofolate derivatives in the intestine	**Orally absorbed.** Excretion through renal elimination	Toxicity mainly related to the co-administered compounds Non-emetogenic		
Raltitrexed Tomudex ®	Competitive inhibition of thymidylate synthase Activity is **S-phase** specific	Polyglutamated by cellular folylpolyglutamate synthase (FPGS). Polyglutamation increase the binding affinity of Raltitrexed to TS.	**IV infusion.**	**GI disturbances. Myelosuppression** Hepatic disturbances are rare but could be fatal Low to moderate emetogenicity	**1.Increase TS levels** **2.Decrease poly-glutamation** **3.Impaired intra-cellular uptake**	

Anti-Metabolites: pyrimidine analogs						
Fluorouracil (5-FU) Adrucil ® Fluoroplex ®	Inhibits DNA synthesis by inhibiting thymidine synthesis. FdUMP forms a ternary complex with thymidylate synthase and methylene tetrahydrofolate Activity is **S-phase** specific	Activated in target (tumor) cells to FdUMP by various metabolic pathways	Variable oral absorption. Usually **administered IP or IV (bolus, infusions).** 80% catabolized by liver and excreted as respiratory CO2.	**GI disturbances** **Myelosuppression** **Cardio-toxicity** **Palmar-plantar erythro-dysesthesia** Rarely emetogenic Mild nausea and vomiting.	**1. Decreased level of thymidylate synthase (target)** **2. Decreased concentration of MTHF (cofactor for ternary complex)** **3. increase expression of anti-apoptotic proteins**	Active drug is metabolized by **dihydro-pyrimidine dehydro-genase (DPD)** to inactive metabolites**. Deficiency of DPD cause severe toxicities.**
Capecitabine Xeloda ®		Metabolized to 5'deoxy-5-fluorocytidine in liver, and activated to FdUMP in target cells	Oral administration, recommended after food. **Capecitabine is an orally available prodrug of 5-FU**			
Cytarabine (Cytosine Arabinoside, Ara-C) Cytosar ®	As an analog to cytidine, Ara-C is incorporated into DNA. Incorporation causes chain termination. Also inhibits DNA polymerase in replication and repair functions Activity is **S-phase** specific	Activated intracellularly to cytosine arabinoside triphosphate	Low oral bioavailability**. IV, SC and IT administered.** Rapid and extensively metabolized by cytidine deaminase to inactive metabolites. Excretion of Ara-C and metabolite chiefly through renal elimination	**Cerebellar toxicity** **Myelosuppression** **Ocular toxicity** Pulmonary edema Fever, Flu-like symptoms **High emetogenicity** is dose-related	**1. Increased metabolism by cytidine deaminase** **2. decreased import of drugs** **3. increase survival pathway proteins expression**	

Gemcitabine Gemzar ®	Analog to cytidine, Gemzar is incorporated into DNA. Incorporation causes chain termination. Also inhibits DNA polymerase in replication and repair functions Activity is **S-phase** specific	Activated intracellularly to dFdCTP	**IV infusion.** Rapid and extensively metabolized by cytidine deaminase to inactive metabolites. Elimination mainly through renal clearance.	**Myelosuppression** **Hemolytic uremic syndrome** Pulmonary toxicity is rare but could be severe. Elevated hepatic enzyme with unclear clinical significance. Low to moderate emetogenicity	**see above for Ara-C**	
Topoisomerases Enzyme Inhibitors						
Irinotecan Camptosar ®	Inhibition of Topoisomerase I **Cytotoxicity is S-phase** specific	**Prodrug,** activate by Carboxy-esterase	**IV infusion**, irinotecan is rapidly converted to its active metabolite SN-38. Both parent drug and SN-38 are highly protein-bound. Hepatic metabolism by CYP3A and the glucuronidation of SN-38 are clinically important.	GI , **life-threatening diarrhea**. **Cholinergic Syndrome induced abdominal pain**. Myelosuppression **High-moderate emetogenicity**	**1. Over-expression of MRP drug efflux pump.** 2. mutations in Topo I 3. Increased DNA repair activities	**UGT enzyme (glucuronidation) poly-morphism determines the clinical use of irinotecan**

Etoposide Vepesid ® Etopophos ®	Inhibition of Topoisomerase II by formation of a ternary complex between Topo II, drug and DNA. Activity is **S and G2 phase** specific.		**Oral or IV (preferred).** 40% of administered dose is excreted intact. Extensively bound to plasma proteins. Reduction in serum albumin will increase toxicities of etoposide.	**Myelosuppression** **Congested heart failure/myocardial infarction** Induces Type I Hypersensitivity Reactions Low to moderate emetogenicity	1. **P-glycoprotein over-expression** 2. mutation or reduced expression of Topo II 3. mutation or loss of function of p53	**Secondary leukemia** due to drug treatment seen in childhood acute lympho-blastic leukemia (ALL) patients
Microtubule Inhibitors						
Vinblastine Velbe ®	Bind to specific site of β-tubulin, preventing the polymerizaton of tubulins to form microtubule. Cells are arrested in mitosis. Activity specific for **M-phase**		**IV infusion.** Variable plasma protein binding. Drug is excreted in both urine and feces.	**Myelosuppression** GI disturbances **Peripheral neuropathy** **Brochospasm** Tissue necrosis due to extravasation rarely emetogenic	1. **Increase expression of P-glycoprotein and/or the MRP drug efflux pumps** 2. mutations in β-tubulin binding sites	Vinblastine is **lethal if injected IT**
Vincristine Oncovin ® Vincasar ®			**IV infusion.** Vincristine is metabolized by CYP3A and excreted primarily in feces	Neurotoxicity. **Peripheral neuropathy.** alopecia Myelosuppression less common than in vinblastine non-emetogenic		Vincristine is **lethal if injected IT**

Paclitaxel Taxol ®	Binds to β-tubulin and promote the stability of microtubule polymers. Cells are arrested in metaphase of mitosis. Activity is specific for **M-phase**		Not absorbed orally. **Administer by IV infusion, or by IP**. Hepatic metabolism (CYP2C8) and biliary secretion account for majority of elimination	**Myelosuppression** **Peripheral neuropathy** **Hypersensitivity Reactions** **CVS toxicity: Bradycardia and hypotension** Low-moderate emetogenicity	1. **Increased expression of P-glycoprotein** 2. Mutations in β-tubulin 3. increase expression of survivin, an anti-apoptotic factor	Severe hyper-sensitivity to paclitaxel could be minimized by pretreatment with cortico-steroid
Docetaxel Taxotere ®	Higher affinity to β-tubulin than paclitaxel. Stabilized microtubule formation, arrested cells in mitosis. Activity is **M-phase specific**		**Administer by IV infusion.** Clearance by CYPA4/5. Excretion through biliary/fecal elimination	**Myelosuppression** **Pulmonary toxicity** Less incidences of hypersensitivity than paclitaxel Low emetogenicity		**Wide inter-patient variability due to CYP3A4 poly-morphism**

Genotoxic Agents

Drug	Mechanism of Action	Activation	Pharmacokinetics	Toxicities	Resistance	Notes
Alkylating Agents: Nitrogen Mustards						
Cyclophosphamide Cytoxan® Procytox®	**Alkylation of nucleophilic moieties on DNA and protein**	**Prodrug, activated by CYP2B6**	**Absorption: oral or IV** Elimination: hepatic metabolism (CY3A4, ADH, GSH and others), half-life of parent drug ~7hours **High emetogenicity is dose related**	**Bone marrow**, **neurotoxicity** mucosal, GI , genitourinary tract epithelium, hair follicles **Cardio-toxicity at high doses Hemorrhagic cystitis** can be relieved by **coadministration of mesna**	**1. increased glutathione conjugation** **2. increased metabolism by aldehyde dehydrogenase** **3. increase DNA repair by MGMT**	Inter-patient variability of activation and toxicity **Secondary urinary bladder and hemato-logical cancers**
Ifosfamide Ifex ®	**Oxazophosphorine alkylating agent. Ifosfamide interferes with DNA metabolism through formation of DNA-DNA crosslinks**	**Prodrug, activation in the liver by hepatic enzyme, mainly CYP3A4, and also CYP2C9**	**Administered by IV infusion.** Elimination: renal (up to 50% unchanged drug) and through hepatic metabolism. Ifosfamide is a major substrate of CYP3A4. half-life of parent drug ~8hours	**Bone marrow**, **neurotoxicity,** urotoxicity and nephro-toxicity **hemorrhagic cystitis** low-moderate emetogenicity **coadministration of mesna**	**1. increased glutathione conjugation** **2. increased metabolism by aldehyde dehydrogenase** **3. increase DNA repair by MGMT**	different pharmaco-kinetics parameters from cyclo-phosph-amide may explain its altered efficacy and toxicity profiles

Mesna Uromitexan ®	**Prevention of hemorrhagic cystitis by reacting with acrolein (a metabolite of cyclophosphamide) to form stable, non-urotoxic compounds**		**50% oral bioavailability**; drug is rapidly cleared from plasma and converted back to parent drug in renal tubules before secretion into urine for its protective function	Mild at clinical doses not emetogenic		Half-life of mesna is shorter than cyclo-phosphamide; needs continuous infusion or multiple doses for protective effects
Platinum Compounds						
Cisplatin Platinol® Platinol-AQ®	**Inter and intra-strand DNA crosslinking;** **N7 of guanine is a particularly active site**	**Parent drug is activated by hydrolysis.** Quick kinetics.	**mainly IV and IP in special applications;** cisplatin is 90% protein bound; unbound drug is rapidly cleared from plasma and excreted by the kidney	**Myelosuppression nephrotoxicity**, peripheral sensory neuropathy, **ototoxicity with cumulative drug dose and is irreversible**, nerve dysfunction **Highly emetic**	1. **reduced intracellular drug concentration** **2. increased capacity of glutathione and/or other sulfhydryls to inactivate drugs** **3.over-expression of nucleotide excision repair (NER) genes**	Synergy with etoposide
Carboplatin Paraplatin ® ParaplatinAQ ®		**Activated by hydrolysis** to form reactive platinum compound. Conversion is much slower than cisplatin	**IV infusion.** Majority of parent drug in unbound form; reactive platinum metabolite is 90% protein bound; majority of drug is eliminated by renal excretion	Carboplatin is less nephrotoxic and ototoxic than cisplatin; **myelosuppression,** nausea and vomiting **High-moderate emetic**		Effective alternative to cisplatin in patients with impaired renal function.

Oxaliplatin Eloxatin ®		**Parent drug is activated by hydrolysis** to form reactive Pt compound.	**IV only**; short half-life in plasma and rapidly redistributed; renal excretion	**Peripheral sensory neuropathy**, **anemia**, diarrhea, myelosuppression, and renal toxicity **High-moderate emetic**		Synergy with 5-FU and irinotecan.
Anthracyclines Antibiotics						
Doxorubicin Adriamycin ®	**1. Formation of tripartite complex with Topo II and DNA** **2. Intercalates DNA and inhibits transcription and replication** **3. Formation of free radicals and induced oxidative stress**		**IV** bolus and IP in special applications; excreted by a combination of hepatic metabolism (aldo-keto reductase) and biliary excretion mechanism.	Myelosuppression, **congestive heart failure** **dose-related high moderate emetogenicity**	**1. over-expression of P-glycoprotein drug efflux pump.** **2. decreased Topo II activity** **3. increased glutathione peroxidase metabolism**	**Con-comitant administration of dexrazo-xane may reduce cardiac damage**
Epirubicin Pharmorubicin ® Ellence ®			**IV bolus administered.** Extensive hepatic metabolism	Reduced cardiac toxicity compared to doxorubicin; **Myelosuppression** **dose-related high moderate emetogenicity**		

Molecular Targeted Anti-Cancer Chemotherapeutic Agents

Small Molecule Tyrosine Kinase Inhibitor					
Agents	**Mechanism of Action**	**ADME**	**Toxicities**	**Resistances**	**NOTES**
Imatinib Gleevec®	**Inhibits BCR-Abl tyrosine kinase.** Competitive binding at the ATP binding site leads to inhibition of downstream phosphorylation of protein targets. Also inhibits tyrosine kinase for platelet-derived growth factor and c-Kit. New congeners to overcome TKI resistance include nilotinib, dasatinib, bosatinib and **ponatinib (only congener active against T315I-TK mutation)**	**Orally administered.** 98% bioavailability 75% oxidized by CYP3A4/5; excreted by both renal and fecal routes	**Myelosuppression** **Edema** **Hepatic disturbances,** severe skin reactions HBV reactivation	**1. mutation in tyrosine kinase (particularly T315I)** **2. amplifi-cation of BCR-Ab** **3. increase drug efflux**	**Interpatient variability and drug interaction must be considered due to CYP3A4 involvement.**
Gefitinib Iressa®	Epidermal growth factor (EGFR) tyrosine kinase inhibitor, **competitively inhibits ATP binding**	**Orally administered**. 60% bioavailability 90% plasma protein bound; extensive hepatic metabolism via CYP3A4; excreted via both renal and fecal routes.	**Diarrhea, nausea and vomiting;** interstitial lung disease is rare but fatal; **QT prolongation;** infusion-related toxicity; skin rash	**1. KRAS mutations** **2. HER-1-TK mutations (particularly T790M)** **3. drug efflux increase**	Low response rate in clinical use to date; perhaps EGFR is not indispensable for tumor survival
Vemurafenib Zelboraf®	Competitive inhibitor of BRAF tyrosine kinase. Selectively suppresses cellular proliferation in tumor cells expressing mutated (V600E) BRAF protein.	**Orally administered.** extensive hepatic metabolism via CYP3A4; excreted via fecal route.	**Hepatic injury, and skin toxicity.** **Acute renal injury** **QT-prolongation** radiation sensitivity pancreatitis and hypersensitivity reactions	**1. MEK1 mutations** **2. activation of IGF1R and/or PDGFRβ**	Drug induced **cutaneous squamous cell carcinomas** in up to 25% patients

Monoclonal Antibodies					
Trastuzumab Herceptin®	Recombinant DNA-derived humanized monoclonal antibody (IgG1); it binds to the epidermal growth factor receptor 2 (HER2); HER2 is over-expressed in 25-30% of cases of Breast Cancers	**IV infusion;** degradation through irreversible receptor binding. Half-life is 5.8-21 days low emetogenicity	**Cardiomyopathy (especially in combination with anthracyclines),** infusion-related toxicity(fever, chills, nausea, dyspnea, rashes)	**Increases EGFR dependent signal transduction activity**	
Bevacizumab Avastin®	Monoclonal antibody (IgG1) that binds to the vascular endothelial growth factor (VEGF) and prevents the activation of VEGF receptor-mediated endothelial cell proliferation; **inhibition of angiogenesis** will delay tumor growth and prevent metastatic disease progression	**IV infusion**; administered every two weeks and has an estimated half-life of 20 days rare emetogenicity	**GI perforations, hemorrhage,** impaired wound healing, severe **dose-dependent hypertension**, proteinuria	**Increased activities of alternate angiogenesis pathways, bypassing VEGF**	Adverse drug reaction are unique for mAb and potentially serious.
Cetuximab Erbitux®	Recombinant, chimeric monoclonal antibody (IgG1) directed against the epidermal growth factor (EGFR, HER1). Activates the complement-mediated cell toxicity, and prevents the activation of EGFR, lead to its anti-cancer effects.	**IV infusion.** Half life range from 2.6 to 9.5 days low emetogenicity	**Acne-like rash** that could lead to Rx termination. May cause cardio-pulmonary arrest and interstitial lung disease in small percent of patients	**Increase signal transduction through the increase of EGFR1 copy number, or switch to the alternate HER2/neu protein signal transduction pathway**	**KRAS and BRAF (oncogenes) mutational status** impacts therapeutic usefulness of these monoclonal antibodies
Pani-tumumab Vectibix®	Fully humanized monoclonal antibody (IgG2) directed against the epidermal growth factor (EGFR, HER1). Receptor target-mediated saturable binding to EGFR and subsequent internalization and degradation.	**IV infusion.** Half life range from 3.6 to 10.9 days low emetogenicity	**Acne-like rash** that could lead to termination of therapy. Acute renal failure may present in patients with dehydration from severe diarrhea		

Monoclonal antibodies in Immune Checkpoint therapies					
Ipilimumab Yervoy®	Fully humanized monoclonal antibody (IgG2) directed against CTLA4	**IV infusion over a period from 30-90 min**	Immune–mediated adverse reactions, sometimes fatal, can involve any organ system. GI tract, liver, skin, endocrine, and nervous systems are most commonly involved. Diarrhea, bloody stool, liver enzyme elevations, rash, and endocrino-pathologies must be considered immune-mediated.	**mutations and disruptions of tumor IFN-γ pathway**	Signs and symptoms suggestive of immune-related reactions may be nonspecific. Immune-mediated toxicities have been reported, even after discontinuation of the drug.
Nivolumab Opdivo®	Fully humanized monoclonal antibody (IgG2) directed against PD-1	**IV infusion over 60 min**		similar mutation profiles as seen in ipilimumab resistance, but longitudinal data needed for conclusive remarks	
Pembroli-zumab Keytruda®	Fully humanized monoclonal antibody (IgG4) directed against PD-1	**IV infusion over 30 min**	**severe infusion-related reactions** in addition to immune-mediated adverse reactions		