CHEMOTHERAPEUTIC AGENTS

Actinomycin D
MOA: antitumor antibiotic
Indications: Germ cell tumor
Pharmacokinetics: metabolized in liver and excreted in bile (up to 50%); $t_{1/2}$ = 30-40_
Dosing:
Toxicity: leukopenia and thrombocytopenia (nadir @ 3 weeks)

Bleomycin
MOA: antitumor antibiotic
Indications: ovarian germ cell tumors
Pharmacokinetics: 50-70% eliminated by kidneys unchanged and cannot be removed by hemodialysis; $t_{1/2}$ 2-5_ with normal CrCl (up to 30_ with renal failure)
Dosing:
Toxicity: anorexia; **interstitial pneumonitis and pulmonary fibrosis** are related to total cumulative dose (> 400u) and manifest by decreased DCO_2.

Carboplatin
MOA: heavy metal alkylating-like agent
Indications: epithelial ovarian cancer
Pharmacokinetics: 60-70% excreted unchanged in urine; $t_{1/2}$ 2.5-6_
Dose (total mg) = Target AUC (6-7) x (GFR + 25)
Toxicity: **thrombocytopenia** is dose limiting; neutropenia; N/V; abnormal LFT (20-30%); asthenia (44%)

Cisplatin
MOA: heavy metal alkylating-like agent
Indications: epithelial ovarian cancer; cervical caner
Pharmacokinetics: 90% bound to plasma proteins within 2-4_ of dosing; 20-45% excreted unchanged by kidneys; $t_{1/2}$ 60-90_
Dosing:
Toxicity: leukopenia and thrombocytopenia; N/V; diarrhea; anorexia; neophrotoxicity is dose related; **peripheral sensory neuropathies** are common and dose limiting when cumulative dose exceeds 400 mg/m^2; **hypomagnesemia**; SIADH

Cyclophosphamide
MOA: alkylating agent
Indications: Germ cell tumors; Gestational trophoblastic neoplasia
Pharmacokinetics: 75% absorbed by mouth and reaches peak plasma levels within 1_ of dosing; dose reductions are not necessary with renal impairment; $t_{1/2}$ 3-10_
Dosing: with concomitant hydration
Toxicity: leukopenia (nadir 8-14 days); N/V; alopecia; **hemorrhagic cystitis with high doses**; bladder cancer when total cumulative dose exceeds 20,000 mg.

Docetaxel (Taxotere)
MOA: antimicrotubule agent; promotes the assembly of tubulin and inhibits microtubule depolymerization; bundles of microtubules accumulate and interfere with mitosis
Indications: epithelial ovarian cancer
Pharmacokinetics: $t_{1/2}$ 11_; 94-97% protein bound; metabolized by liver; eliminated primarily in feces
Dosing:
Toxicity: **Neutropenia** often dose limiting; mucositis (56%); **total alopecia**; fluid retention

Doxorubicin (Adriamycin), Doxorubicin-HCl liposomal injection (Doxil)
MOA: anthracycline antitumor antibiotic
Indications:
Pharmacokinetics: 70% bound to plasma proteins; metabolized in liver to active metabolite, doxorubicinol; 40-50% of doxorubicin and doxorubicinol is eliminated by the biliary route and 4-5% in the urine; $t_{1/2}$ 18-30_
Dosing:
Toxicity: leukopenia (dose limiting, nadir 10-14d); N/V; total alopecia; **cardiomyopathy** is related to total cumulative dose (risk greatest when total dose > 550 mg/m^2). *Serial monitoring of LVEF is indicated. Doxorubicin is discontinued when there is an absolute decrease in LVEF by 10%.* Cardiomyopathy after Doxil has occurred in < 1% of patients.

Etoposide
MOA: plant alkaloid (topoisomerase II inhibitor)
Indications:
Pharmacokinetics: 25-75% absorbed orally; peak plasma levels 1-1.5_ after dosing. Metabolized by liver and excreted in bile (10-15%) and urine (30-40%); $t_{1/2}$ 7-14_
Dosing: 50 mg/m^2 po x 21d
Toxicity: Granulocytopenia, nadir 7-14d; N/V common with oral dosing

5-flourouracil
MOA: pyrimidine antimetabolite

Indications: radiosensitizer for cervical radiotherapy
Pharmacokinetics: After IV administration, drug is metabolized to active metabolites; 22-45% is metabolized by the liver and 15% is excreted unchanged in the urine; $t_{1/2}$ = 10-20"
Dosing:
Toxicity: more severe in patients with dihydropyrimidine dehydrogenase deficiency; mucositis, **diarrhea**

Gemcitabine (Gemzar)
MOA: antimetabolite (nucleoside analog); converted to gemcitabine diphosphate which inhibits the activity of ribonucleotide reductase and production of cellular nucleotides. Gemcitabine triphosphate inhibits DNA synthesis by competing with cytidine triphosphate for incorporation into DNA
Indications:
Pharmacokinetics: peak levels 30" after IV infusion; $t_{1/2}$ = 49-94"; eliminated almost entirely in the urine
Dosing: 1000 mg/m^2 qwk x 7 wks
Toxicity: **neutropenia**, transaminitis, peripheral edema (30%), **proteinuria** (32%), hematuria (23%)

Ifosphamide
MOA: alkylating agent
Indications:
Pharmacokinetics: metabolized in liver and 15-56% is excreted unchanged in the urine; $t_{1/2}$ = 7-15_
Dosing: 1000-1200 mg/m^2/d; must be given with Mesna; usual dose of Mesna is 20% of the Ifosphamide dose
Toxicity: **myelosuppression** (dose-limiting) with leukopenic nadir 7-10d; N/V; alopecia (83%)

Medroxyprogesterone acetate
MOA: progestin
Indications: adjunctive therapy and palliative treatment of inoperable, recurrent, or metastatic endometrial cancer
Pharmacokinetics: peak plasma levels within 1-2_. Oral bioavailability 10%; $t_{1/2}$ = 14-60_
Dosing: 400-1000 mg IM weekly
Toxicity: menstrual changes

Megestrol acetate (Megace)
MOA: progestin which interferes with replenishment of cytoplasmic estrogen receptors, thereby decreasing the quantity of estrogen receptors
Indications: endometrial cancer
Pharmacokinetics: peak plasma levels 1-3_ after oral ingestion; metabolized by liver; $t_{1/2}$ = 15-20_
Dosing: 40-320 mg/d
Toxicity: hypercalcemia with high doses; IDDM

Methotrexate
MOA: antimetabolite (anti-folate)
Indications: Germ cell tumors; gestational trophoblastic neoplasia
Pharmacokinetics: 90% eliminated unchanged in urine; $t1_{/2}$ = 3_
Dosing: 50 mg/m^2 IM
Toxicity: **leukopenia** and **thrombocytopenia**; mild transient transaminitis

Paclitaxel (Taxol)
MOA: plant alkaloid (antimicrotubule agent)
Indication: epithelial ovarian cancer
Pharmacokinetics: 95-98% protein bound and metabolized to 7-epitaxol; $t_{1/2}$ = 5_
Dosing 135 mg/m^2 prior to dosing of Cisplatin because of the increased incidence of sever leukopenia if Cisplatin is given first
Toxicity: **neutropenia** (dose limiting), mucositis, alopecia; **peripheral neuropathy**, more frequent with longer infusions, with doses > 170 mg/m^2.

Topotecan
MOA: topoisomerase I inhibitor
Indication: epithelial ovarian cancer after failure of initial and second-line therapy
Pharmacokinetics: $t_{1/2}$ = 2-3_
Dosing: 1.5 mg/m^2/d IV x 5d
Toxicity: **severe neutropenia** (81%); severe N/V (10%); diarrhea (25-42%); total alopecia

Vinblastine
MOA: plant alkaloid (tubulin inhibitor)
Indication:
Pharmacokinetics: metabolized by liver to desacetylvinblastine; $t_{1/2}$ = 20_
Dosing: 6-10 mg/m^2 q2-4 weeks
Toxicity: dose limiting leukopenia

Vincristine (Oncovin)
MOA: plant alkaloid (tubulin inhibitor)
Indication: germ cell tumor; gestational trophoblastic neoplasia
Pharmacokinetics: metabolized by the liver and 40-70% is excreted in the bile; $t_{1/2}$ = 85_

Dosing: 0.5-1.4 mg/m^2
Toxicity: alopecia (12-45 %); mild transient transaminitis; peripheral and autonomic neuropathy;