

MANAGING COMPLICATIONS OF CHEMOTHERAPY
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The primary goal for most anticancer agents is to injure DNA or prevent production of RNA and proteins coded by DNA. This might lead to a decreased ability of tumor cells to replicate, and ideally, cell death. Unfortunately, rapidly proliferating normal cells such as bone marrow progenitor cells, gastrointestinal epithelial cells, hair follicles and germ cells can also be adversely affected by chemotherapy drugs. Toxicities to normal tissues limit the dose of drugs which can be given to patients. Therapeutic index is the dose of a drug required to produce a given level of damage to normal tissues divided by the dose of the drug required to produce anticancer effects. Optimizing the therapeutic index is the goal of clinical chemotherapy.

While this handout cannot be completely inclusive of all potential toxicities associated with anticancer agents, it should serve as a basis from which clinicians can develop experience with the various drugs used in veterinary oncology. Whenever unusual symptoms develop subsequent to the administration of chemotherapy, the clinician should be very suspicious of a potential chemotherapy-associated toxicity and should consult an oncologist or textbook for a more complete description.

HEMATOLOGIC TOXICITY

I. Myelosuppression

- A. Represents one of the major dose-limiting toxicities of chemotherapy drugs.
- B. Drugs vary in their potential to suppress the bone marrow (Table)
- C. Progenitors – immature, mitotic pool, most chemosensitive.
- D. Stem cells – mostly non-proliferating, relatively resistant to chemotherapy toxicity. Replenish mitotic pool.
- E. Precursors + differentiated cells – non-proliferating. Pool produces mature cells to circulation for 5-10 days.

TABLE. CLASSIFICATION OF ANTINEOPLASTIC AGENTS BY DEGREE OF MYELOSUPPRESSION WHEN USED AS SINGLE-AGENTS.

SEVERE (<1,000 neutrophils/μL)	MODERATE (1-2,000 neutrophils/μL)	MILD-NONE (>2,000 neutrophils/μL)
carboplatin	actinomycin	bleomycin
CCNU	cisplatin	chlorambucil
cyclophosphamide	cytosine arabinoside	corticosteroids
doxorubicin	dacarbazine	L-asparaginase*
mitoxantrone	docetaxel	streptozotocin
	hydroxyurea	vincristine*
	ifosfamide	etoposide
	melphalan	
	mustargen	
	procarbazine	
	vinblastine	
	5-fluorouracil	

* when used in combination, moderate-to-severe myelosuppression might occur presumably due to delayed hepatic clearance of vincristine.

II. Neutropenia

- A. All cells can be affected by anticancer drugs but effect on neutrophils is greatest concern.
- B. Nadir (lowest point in neutrophil count) – usually 5-7 days post-treatment.
 - 1. life span of neutrophils in circulation – approximately 6 hours.
 - 2. precursor pool provides cells for 5-10 days.
 - 3. neutrophil count slowly declines until nadir.
 - 4. most often count returns to normal 48-72 hrs post-nadir.
- C. Exceptions:
 - 1. carboplatin – variable nadir (dogs, 7-28d; cats, 14-21d).
 - 2. CCNU – cats, variable nadir (7-28d).
 - 3. prior therapy
 - 4. individual patient variation!
- D. Risk of sepsis:
 - 1. high risk if absolute neutrophil count $< 1,000/\mu\text{L}$. (absolute count is important – not total or %).
 - 2. primary source of infection is GI tract.
 - a. chemotherapy-induced mucosal damage allows invasion by opportunistic gram-negative bacteria (*Escherichia*, *Klebsiella*, *Pseudomonas*). Gram-positive cocci and anaerobes less common.
 - 3. clinical signs – fever, weakness, shaking/shivering, brick-red mucus membranes, tachycardia, tachypnea, coughing, vomiting, diarrhea
 - 4. cardinal signs of inflammation may be absent due to insufficient numbers of neutrophils to participate in the inflammatory process.
- E. Prevention
 - 1. pre-treatment CBC – general rule of thumb, prior to myelosuppressive therapy, should start with normal neutrophil count.
 - 2. monitor CBC at expected nadir.
 - 3. dose-reduction by 25% next time drug is given is absolute neutrophil count $< 1,000/\mu\text{L}$ at nadir.
 - 4. caution with small and obese dogs.
 - 5. consider prophylactic antibiotic (sulfadiazine-trimethoprim 15 mg/kg PO BID) prior to receiving first treatment of a severely myelosuppressive drug
 - 6. avoid overlapping myelosuppressive drugs.

III. Thrombocytopenia

- A. Life span of platelets in circulation is approximately 5-6 days.
- B. Nadir may occur 7-14 days post-treatment.
- C. Thrombocytopenia is rarely severe enough to cause spontaneous bleeding unless coupled with gram negative septicemia, DIC or vasculitis.
- D. Exceptions:
 - 1. carboplatin – dogs, severe thrombocytopenia can occur.
 - 2. CCNU – dogs, cumulative thrombocytopenia can occur.

IV. Anemia

- A. Life span of erythrocytes in circulation is 110-120 days (dog) and 70 days (cat).
- B. Anemia post-chemotherapy is common but only after cumulative treatments.
- C. Anemia is rarely severe and rarely of clinical significance.
- D. Exceptions
 - 1. hydroxyurea – drug of choice for polycythemia vera and CML. May cause severe anemia (often macrocytic anemia)

V. Management of Neutropenic Patients

A. Afebrile neutropenia

1. can be treated as an outpatient. generally asymptomatic.
2. prophylactic antibiotics:
 - a. if absolute neutrophil count $< 1,000/\mu\text{L}$ at the nadir.
 - b. if vague, non-specific signs and count $1-2,000/\mu\text{L}$.
 - c. sulfadiazine-trimethoprim (Tribrissen®, 15 mg/kg q12h PO x 5-7d).
 - broad-spectrum & spares normal urease-producing gut flora which provide local gut protection.
 - d. owners should monitor rectal temperature (q12h x 48h) and if fever develops or patient condition deteriorates, aggressive diagnostics/therapeutics recommended.
3. 25% dose-reduction next time drug is given if absolute neut count $< 1,000/\mu\text{L}$ at nadir.

B. Febrile neutropenia

1. Fever in a neutropenic patient constitutes a medical emergency.
2. Search for septic focus:
 - a. thorough history and PE
 - b. CBC, chemistry panel, UA
 - c. thoracic radiographs – without supporting PE findings or history, low yield.
 - d. blood cultures and urine cultures – results take many days and knowing colony flora is unlikely to make a tremendous impact on initial treatment since broad-spectrum antibiotics should be started immediately.
3. Management:
 - a. hospitalization for IV fluid support and antibiotics.
 - b. discontinue anticancer drugs.
 - if receiving corticosteroids – gradually taper or consider physiologic doses depending on duration and dosage currently being administered.
 - c. antibiotics:
 - always IV to avoid limitations of poor absorption across intestinal epithelium.
 - empirical choices: cephalosporin or extended-spectrum penicillin and aminoglycoside or fluoroquinolone.
 - treat until neutrophil count improves to near normal and patient is clinically normal and afebrile for at least 48hrs
 - discharge with broad-spectrum antibiotics (cephalosporin or penicillin and fluoroquinolone or sulfadiazine-trimethoprim.
 - d. granulocyte colony-stimulating factor (G-CSF, Neupogen®; 5 $\mu\text{g}/\text{kg}$ SQ q24h)
 - regulates production, maturation and function of neutrophils.
 - primary use is to administer G-CSF 24-48h after highly myelosuppressive chemotherapy to decrease the duration and depth of neutropenia.
 - Neutropenic state causes upregulation and production of G-CSF so serum concentrations are actually higher than before neutropenia – however, dogs with cancer will have lower G-CSF concentrations at their nadir than a healthy dog that was given chemotherapy.
 - Neutrophil oxidative burst is decreased in septic dogs.
 - Evidence suggests G-CSF can actually improve neutrophil function
 - giving G-CSF to neutropenic patients that are already febrile might speed neutrophil recovery and reduce hospitalization.
 - data from human literature does not show consistent clinical benefit and G-CSF is not always recommended as an adjunct to empirical antibiotic therapy.
 - also, currently only human G-CSF is available and dogs might develop neutralizing antibodies if prolonged courses are given (i.e. $>3\text{wks}$).

GASTROINTESTINAL TOXICITY

I. Mechanism

- A. Certain drugs have a higher incidence of adverse GI effects (Table).
- B. In the individual patient, all drugs should be considered to have the potential to cause severe GI toxicity.
- C. Mechanism of GI toxicity is multifactorial:
 1. direct damage to GI mucosal epithelial cells.
 2. stimulation of chemoreceptor trigger zone (CRTZ; floor of 4th ventricle) via neurotransmitters.
 3. stimulation of medullary emetic center via neurotransmitters (especially neurokinins (NK1) like substance P). Abolishing vomiting at the level of the emetic center likely has a role in controlling emesis due to a variety of causes.
 4. local GI tract irritation to stimulate GI neurotransmitter receptors and subsequent activation of vomiting center via vagus and sympathetic nerves
 - a. neurotransmitters: serotonin, neurokinin (sub P), dopamamin, histamine, norepinephrine
 - b. serotonin released from enterochromaffin cells of the GI tract (acute vomiting).
 - c. other neurotransmitters (delayed vomiting).
 - d. neurokinins (substance P) found in nuclei of vomiting center – central role as a neurotransmitter in sensory neurons and also in the afferent pathway of the vomiting reflex. NK1 receptor antagonists (maropitant, Cerenia 1 mg/kg SQ q 24h x 5d or 2 mg/kg PO q24h x 5d) appear to have a major role controlling both acute and delayed emesis. Abolishing vomiting at the level of the emetic center likely has a role in controlling emesis due to a variety of causes.

TABLE. EMETIC POTENTIAL OF CHEMOTHERAPY DRUGS.

HIGH	MODERATE	LOW
cisplatin	actinomycin	bleomycin
dacarbazine	carboplatin	chlorambucil
streptozotocin	cytosine arabinoside	CCNU
docetaxel	doxorubicin	cyclophosphamide
	etoposide	ifosfamide
	methotrexate	L-asparaginase
	mustargen	melphalan
	procarbazine	mitoxantrone
	vinblastine	5-fluorouracil
	vincristine	

Timing of GI Toxicity

A. Acute

1. vomiting during chemotherapy is uncommon.
2. Exceptions: cisplatin, streptozotocin, dacarbazine. Occasionally doxorubicin, actinomycin, cyclophosphamide.

B. Delayed

3. Most patients. Begins 2-5 days after treatment.
4. Anorexia – common in cats, especially after vincristine and may be related to peripheral neurotoxic effects on the GI tract leading to paralytic ileus.
5. Vomiting and diarrhea – related to damage to rapidly dividing mucosal epithelial cells.
6. Pancreatitis – very rare but may be the cause of delayed GI signs. Drugs implicated include doxorubicin, L-asparaginase, methotrexate, azathioprine, corticosteroids.

II. Management of GI Toxicity

- A. GI symptoms associated with a fever may be more serious and can be the first signs of sepsis.
- B. Patients that experience severe GI toxicity should have 25% dose-reduction next time drug is given.
- C. Anorexia
 1. Vincristine – generally due to ileus. Most animals respond to metoclopramide
 2. Cats – cyproheptadine (Periactin®, 2-4mg/cat q12-24h) can be fairly effective. Mirtazapine (alpha-2 antagonist, nonselective serotonin antagonist – cats 1/8 to 1/4 of 15-mg tab q 3d – more information is needed)
 3. Cisplatin – cyproheptadine (Periactin®, dog, 0.5mg/kg q12h) can be fairly effective if non-responsive to metoclopramide. Maropitant (NK1 antagonist; Cerenia®) might have a role for anorexia (1 mg/kg SQ q 24h x 5d or 2 mg/kg PO q24h x 5d).
 4. Can try H2-antagonists or cyproheptadine
 5. Anytime anorexia is prolonged, consider hospitalization for fluid/nutritional support.
- D. Vomiting – mild, self-limiting
 1. NPO x 12-24h, water trial, introduce bland foods/small meals.
- E. Diarrhea – mild, self-limiting
 1. No food x 12h, introduce bland foods/fiber.
 2. Pepto-Bismol® (1 Tb per 15lb q8h or 1 tablet per 15lb divided q12h) – particularly effective for hemorrhagic colitis associated with doxorubicin.
 3. Loperamide (Imodium®, 0.08 mg/kg q6-8h)
- F. Severe Vomiting or Diarrhea
 1. Hospitalization for fluid, antiemetic, prophylactic antibiotics and possibly nutritional support.
 2. GI symptoms associated with a fever may be more serious and can be the first signs of sepsis.
 3. Fluid support
 - a. replacement fluids.
 - b. For dogs hospitalized within 36h of receiving cisplatin – 0.9% NaCl fluid of choice. If active drug remains, high chloride environment protects against nephrotoxicity.
 4. Antiemetics
 - a. Metoclopramide (Reglan®) – CRI 2.2mg/kg IV over 24h is preferable.
 - b. Maropitant (Cerenia®) 1 mg/kg SQ q 24h x 5d or 2 mg/kg PO q24h x 5d
 - c. Chlorpromazine (Thorazine®) – 0.5 mg/kg q6h SQ if persistent vomiting.
 - d. Serotonin antagonists (Ondansetron, Zofran®, 0.1 -1mg/kg q12-24 IV, PO; Dolasetron, Anzemet®, 0.6-1 mg/kg q24h IV). Mirtazapine (alpha-2 antagonist, nonselective serotonin antagonist – dogs, 1/4 to 1 full 15-mg tab PO q24hr; cats, 1/8 to 1/4 of 15-mg tab q 3d – more information is needed)
 - e. Butorphanol (Torbugesic®) – 0.4 mg/kg IM administered once during cisplatin and streptozotocin infusion. An additional treatment may prove beneficial for dogs exhibiting severe nausea or acute vomiting within 6-12h of receiving these drugs.
 5. H2-antagonists – ranitidine (2mg/kg BID IV, PO) has prokinetic activity and might have a role for ileus secondary to vinca alkaloids.
 6. Antidiarrheals
 - a. Pepto-Bismol® (1 Tb per 15lb q8h or 1 tablet per 15lb divided q12h) – particularly effective for hemorrhagic colitis associated with doxorubicin.
 - b. Loperamide (Imodium®, 0.08 mg/kg q6-8h)
 - c. Consider opportunistic infections secondary to altered GI flora in patients with prolonged diarrhea or diarrhea nonresponsive to therapy
 - colitis – metronidazole (Flagyl®, 15 mg/kg q12h PO), sulfasalazine (Azulfidine®, 10-15 mg/kg q6-8h PO), tylosin (5-10 (40)mg/kg PO bid)
 - Small bowel diarrhea – rarely r/o salmonella, campylobacter.

CARDIAC TOXICITY

I. Mechanism

- A. Associated with anthracycline drugs – doxorubicin, daunorubicin, epirubicin.
- B. Doxorubicin is most widely used in veterinary oncology.
 - 1. dogs – safe cumulative dose is 180-240 mg/m². Cardiac abnormalities can occur at much lower doses.
 - 2. cats – EKG, echocardiograph and histologic changes are seen however clinical cardiac disease does not seem to be a problem.
- C. Acute cardiac toxicity
 - 1. occurs during or shortly after treatment (uncommon).
 - 2. non-dose dependent.
 - 3. related to histamine-mediated catecholamine release from mast cells during rapid infusion.
 - 4. signs – arrhythmias, hypotension, collapse and other signs of hypersensitivity reaction (see later).
 - 5. almost completely eliminated if drug is given slowly (1mg per min).
 - 6. generics? – higher frequency of acute reactions reported when using generic doxorubicin. This is questionable.
- D. Chronic cardiac toxicity
 - 1. cumulative, dose-dependent.
 - 2. cause is multifactorial but mostly related to free radical damage to myocytes and high peak serum concentrations.
 - 3. irreversible, dilated cardiomyopathy; persistent arrhythmias – days to months following last dose.

II. Prevention of Cardiac Toxicity

- A. Avoid use of doxorubicin if underlying cardiac disease (myocardial disease, arrhythmias).
- B. Limit cumulative dose to 150-180 mg/m².
- C. Cardiac monitoring - echocardiograph
 - 1. breeds at risk – Doberman, Boxer, giant breeds (pre-doxorubicin and during therapy)
 - 2. dogs with murmurs – pre-doxorubicin to rule out myocardial disease vs valvular disease.
 - 3. if > 180 mg/m² cumulative dose
 - 4. cardiac troponin (cTnt) – protein that mediates interaction between actin and myosin. Measurements may allow for early detection of myocardial injury caused by doxorubicin. More information is needed.
- D. Dexrazoxane (Zinecard®) – iron chelator (iron needs to be present for free radical generation to occur). Effectively reduces the cardiotoxicity of doxorubicin. No benefit once cardiac damage has occurred. Expensive.
- E. Anthracycline analogues – other drugs that may prove beneficial if doxorubicin is contraindicated (mitoxantrone, actinomycin).

III. Management of Cardiac Toxicity

- A. Arrhythmias – discontinue drug. Antiarrhythmics as indicated.
- B. Consult with cardiologist regarding cardiac medications.
- C. Overall prognosis is very poor. Changes are irreversible.

HYPERSENSITIVITY REACTIONS

I. Mechanism

- A. L-asparaginase – polypeptide of bacterial origin. Stimulates production of IgE and other immunoglobulins. Ig's mediate acute type I anaphylactic reaction. Delayed reactions a few hours to several days can occur. Higher frequency of reactions if given IV or IP.
- B. Doxorubicin – not immunologically-mediated. Hypersensitivity reaction is related to direct mast cell degranulation and histamine release if the drug is given too quickly. Also, associated more with generic formulations, however, this is questionable.
- C. Taxanes (paclitaxel, docetaxel) – contain chremophor as vehicle, causes massive mast cell degranulation when administered IV.
- D. Etoposide – contains polysorbate 80 as vehicle, causes mast cell degranulation when administered IV.
- E. Idiosyncratic reactions – can potentially occur with any of the other anticancer drugs.

II. Clinical Signs

- A. pruritis, urticaria, cutaneous erythema, agitation, head shaking, facial edema, vocalization, injection-site discomfort, vomiting, diarrhea, hypotension, collapse.

III. Treatment of Hypersensitivity Reactions

- A. Discontinue drug.
- B. Dexamethasone 0.5-1 mg/kg IV
- C. Diphenhydramine (Benadryl®, 2.2 mg/kg IV, IM)
- D. If severe – epinephrine (0.1-0.5ml of 1:1,000 solution IV) and fluid support. If clinical signs do not completely resolve, repeat diphenhydramine.

IV. Prevention of Hypersensitivity Reactions

- A. L-asparaginase – since true immunologic reaction, risk increases w/ prior sensitization. Don't give IV or IP.
- B. Doxorubicin – reaction is related to giving drug too quickly and is minimized/eliminated if given as a slow IV infusion (1mg per minute).
- C. Taxanes and etoposide – not immunogenic so can occur after first dose. Premedication is required.
- D. Premedication: Diphenhydramine and Dexamethasone (0.5mg/kg IM) – 20minutes prior (see above)
- E. If animal has had prior reaction then drug should be discontinued (L-asparaginase) or given with premedication.

UROTHELIAL TOXICITY

I. Mechanism

- A. Drugs – cyclophosphamide, ifosfamide
- B. Mechanism – acrolein and other metabolites cause direct damage to bladder epithelium.
- C. Incidence – cyclophosphamide (dog, 7%; cat, very rare).

II. Clinical Signs

- A. “Sterile hemorrhagic cystitis” – hematuria, stranguria, dysuria, pollakiuria.

III. Prevention of Urothelial Toxicity

- A. Cyclophosphamide
 - 1. force diuresis
 - Furosemide 2.2 mg/kg IV once at time of cyclophosphamide
 - Prednisone – if animal is on prednisone-containing protocol, give cyclophosphamide same day as prednisone.
 - 2. give drug early in morning and allow pet to drink and urinate often x 24h.

- B. Ifosfamide
 1. must be given with specific diuresis protocol.
 2. must give with Mesna (2-mercaptoethane sulfonate) – binds acrolein in the bladder.

IV. **Treatment of Urothelial Toxicity**

- A. Rule out bacterial cystitis as cause of clinical signs – get UA and urine culture.
- B. Discontinue cyclophosphamide – permanently.
 1. consider substituting different alkylating agent (i.e. chlorambucil) or other drug that is appropriate for type of tumor.
- C. Steroids – antiinflammatory doses (0.5 mg/kg q12h PO)
- D. MSM (oral dimethylsulfoxide) – small dogs (1 tab x 5d then ½ tab); large dogs (2 tab x 5d then 1 tab).
- E. Flavoxate (Urispas®) – urinary antispasmodic, dogs 100-200mg q6-8h.
- F. Antibiotics – if secondarily infected.
- G. Intravesicular infusions – rarely indicated but have been done for severe, refractory cases (25-50% DMSO, 1% formalin).

EXTRAVASATION INJURIES

I. **Mechanism**

- A. Vesicant drugs – doxorubicin, daunorubicin, epirubicin, vincristine, vinblastine, mechlorethamine, actinomycin, mitomycin, plicamycin. Other drugs are potential irritants (dacarbazine, etoposide, cisplatin, carboplatin, ifosfamide).
- B. Agents that bind DNA (doxorubicin, daunorubicin, actinomycin)
 1. immediate tissue damage but delayed signs (>10d).
 2. bind DNA, complexes are released from dead cells and bind with DNA of surrounding cells causing persistent, progressive destruction.
 3. further tissue damage by free radicals.
 4. remains in tissues for up to 5 months.
- C. Agents that do not bind DNA (vincristine, vinblastine, mechlorethamine)
 1. chemical irritation, similar to chemical or thermal burn.
 2. signs 1-7d.
 3. shorter duration of tissue destruction and better healing

II. **Prevention of Extravasation Injuries**

- A. Restraint
- B. Do not use veins that have been punctured within 24h.
- C. Proper administration – doxorubicin (catheter), vincristine (butterfly).
- D. Always check for patency.

III. **Treatment of Extravasation Injuries**

- A. All drugs:
 1. stop the injection.
 2. do not remove the butterfly/catheter.
 3. aspirate the drug and 3ml of blood back into the syringe while needle remains in place.
 4. 27g needle to aspirate and withdraw as much subcutaneous bleb as possible.
 5. anecdotal antidotes:
 - infiltrating steroids: not recommended. Inflammation is not part of the etiology and may actually increase toxicity.
 - Sodium bicarbonate: postulated to decrease cellular uptake of doxorubicin (anecdotal).
 6. Prevent self-mutilation
 - Elizabethan collar
 - Topical Synotic® + 1cc Banamine® q12h

C. Vincristine/Vinblastine

1. infiltrate area with saline to dilute extravasated drug.
2. warm compresses to enhance local circulation (q10 minutes every 6hr for 72hr)
3. other: hyaluronidase (reconstituted with saline, inject 150-900u into site) – enhances absorption. Effective for vinca alkaloids, detrimental for doxorubicin.

D. Doxorubicin

1. do not infiltrate!
2. cold compresses (ice) 30min then 15min 4x/d x 3d
3. Dimethylsulfoxide (DMSO) topical q8h for 7-14d. Free radical scavenger rapidly penetrates tissues.
4. administer dexrazoxane (Zinecard) within 3 hrs. Repeat 24 and 48 hours.
5. consider surgical debridement.

E. Mechlorethamine

1. 25% sodium thiosulfate – 1.6ml + 8ml sterile water – inject 5-6ml. Repeat in several hrs.
2. Apply cold compress 6-12 hours.

TABLE. POTENTIAL TOXICITIES OF COMMONLY USED CHEMOTHERAPY AGENTS.

Drug	Myelosuppression			GI			Slough	Hypersensitivity	Other
	Sev	Mod	Mild	Sev	Mod	Mild			
Actinomycin		X			X		X		
Bleomycin			X			X			pulmonary fibrosis
Carboplatin	X				X				
CCNU	X					X			cum. thrombocytopenia; hepatotoxicity, rare renal
Chlorambucil			X			X			rare neurotoxicity (myoclonus)
Cisplatin		X		X					nephrotoxicity, seizures; contraindicated in cats
Cyclophosphamide	X					X			urothelial toxicity, occasional acute emesis
Cytosine arabinoside		X			X				
Dacarbazine		X		X					pain at injection-site
Docetaxel		X			X			X	oral – under investigation; hypersensitivity if IV
Doxorubicin	X				X		X	X	cardiotoxicity
Etoposide			X		X			X	irritant; hypersensitivity if given IV
5-fluorouracil		X				X			neurotoxicity; contraindicated in cats
Hydroxyurea		X							cyanosis (cats); nail slough
Ifosfamide		X				X			urothelial toxicity; renal toxicity
L-asparaginase			X			X		X	potential severe myelosupp. if w/vincristine
Melphalan		X				X			myelosuppression can be prolonged
Mechlorethamine		X			X		X		
Methotrexate			X		X				
Mitoxantrone	X					X			Irritant / slough if extravascular leak
Paclitaxel		X				X		X	palmar-plantar erythrodyesthesia
Procarbazine		X			X				
Streptozotocin			X	X					nephrotoxic; diabetes; rarely hepatotoxic
Vinblastine		X			X		X		
Vincristine			X		X		X		potential severe myelosuppression if w/L-asp.