MICROTUBULE-TARGETING DRUGS

VINCRISTINE/VINBLASTINE
(ONCOVIN®/VINCASAR® PFS™; ALKABAN-AQ®/VELBAN®)

I. MECHANISM OF ACTION

A) During the metaphase period of mitosis, the spindle apparatus forms across the cell. It is made of microtubules of tubulin. The vinca alkaloids bind to tubulin, preventing microtubule assembly, and arrest cell reproduction at metaphase.
B) Binding to tubulin also occurs in nerves, accounting for the neurotoxicity of these drugs.
C) Resistance is due to p-glycoprotein or alteration of the tubulin-binding site.

II. PHARMACOKINETICS

A) Distribution - Poor CNS penetration, but binds extensively to blood elements and especially platelets.
B) Metabolism - Extensive liver metabolism.
C) Elimination - About 70% is eliminated in the biliary tree and 15% in the urine. Elevation of bilirubin of alkaline phosphatase can reflect poor elimination of the vincas.

DRUG	ADJUSTMENT FOR HEPATIC DYSFUNCTION (% OF NORMAL DOSE TO BE ADMINISTERED)						
	Tbili < 1.5	SGOT < 60	Tbili 1.5-3.0	SGOT 60-180	Tbili 3.1-5	SGOT >180	Tbili >5
VINCRISTINE*	100%		50%		Omit		Omit
VINBLASTINE*	100%		50%		Omit		Omit
VINORELBINE**	< 2 mg/dL 100%		2.1 - 3 mg/dL 50%		> 3 mg/dL 25%		Unknown

References: * King PD, Perry MC. Hepatotoxicity of Chemotherapeutic Agents. In: The Chemotherapy Sourcebook, 3rd Edition. Lippincott Williams and Wilkins 2001; **Clinical Pharmacology Online, Accessed 3/30/05.

III. DOSAGE AND ADMINISTRATION

A) Vincristine is usually given IV push but may be given as a CIVI through CVL access.
B) Vinblastine can be given bolus or infused.
C) For nearly all tumors in adults except Hodgkin's disease, the dose of vincristine will be capped at 2 mg per course. Dosing by meter squared will mathematically lead to a higher dose but the dose does not exceed 2 mg in most instances. This approach is to avoid unnecessary neurotoxicity.

IV. TOXICITY

A) Neurologic - Dose limiting side effect for vincristine but less common with vinblastine.

Risk Factors:

Age > 40 years
Short intervals between doses
Concurrent etoposide or radiation therapy
Dose over 2 mg
Cumulative dose

Forms:

Peripheral Neuropathy

- A symmetric and distal disorder affecting motor and sensory function
- Loss of DTR, paresthesias of fingers and toes, decreased strength in the lower extremities, hands, and wrist, leading to foot drop or hand drop. These symptoms may resolve within 2 months after ceasing therapy.

Cranial nerve palsies

- Hoarseness, diplopia, facial palsies.

Autonomic neuropathies

- Paralytic ileus (5%).
- Constipation (30%).
- Urinary retention and arterial hypotension occur rarely.

Treatment- There is no known antidote. Usually it is not necessary to stop therapy for sensory neuropathies. Motor deficits should be assessed relative to the degree of impairment and therapeutic efficacy. Check neurologic function by asking about daily living skills like buttoning clothes, using a fork, or climbing stairs. An EMG or NCS will aid in documenting the disorder.
There is limited information suggesting that leucovorin may reverse or prevent neurotoxicity of vincristine.

B) SIADH.
C) Alopecia.
D) Rarely, dysphagia, Raynaud's phenomenon, and acute MI have occurred.
E) Myelosuppression occurs with vinblastine about day 7-10 after therapy. No significant myelosuppression occurs with vincristine.
F) Hypertension with vinblastine.
G) Vincristine and vinblastine are both vesicants.

V. CLINICAL MONITORING

A) Labs- CBC with differential and platelets, Na, Bili, alkaline phosphatase.
B) History and physical - Urine output, neurological exam, cardiac history, bowel function.
C) Constipation and slowed bowel function can be helped by a bowel stimulant. Regular laxatives/stool softeners must be prescribed.
D) Vincristine reduces phenytoin plasma concentration 50% and erythromycin raises vincristine plasma concentrations.

VINORELBINE
(NAVELBINE®)

I. MECHANISM OF ACTION
Binds to tubulin to prevent microtubule and spindle formation during metaphase. Vinorelbine also interferes with spiral formation of the microtubules, which is different from vincristine or vinblastine. It has less affinity for axonal tubulin, as does vincristine.

II. PHARMACOKINETICS
A) A liquid-filled soft gelatin capsule is under development. Its bioavailability is 24%. Food does not impair absorption.
B) Vinorelbine is very lipophilic and distributes widely. Brain concentrations are small. It is highly (78%) bound to platelets. It is also bound to lymphocytes, red cells, albumin, alpha-1-acid glycoprotein, and lipoproteins.
C) Vinorelbine undergoes extensive metabolism to at least two metabolites, one of which is as active as the parent drug.
D) The parent drug and metabolite are extensively eliminated in the bile. Only 15% passes through the urine.

III. DOSAGE AND ADMINISTRATION
A) Vinorelbine is usually given IV push but may be infused. An oral dosage form is under development.
B) The usual dose is 30 mg/m^2 weekly.
C) For patients with an elevated bilirubin, the dose should be adjusted. If the bili is 2.1-3 mg/dL, give 15 mg/m^2 and for bilirubin over 3 mg/dL use 7.5 mg/m^2.
D) Adjust the dose for neutropenia as well. If the ANC = 1 -1.499 x 10^9/L, give 15 mg/m^2. Hold therapy for an ANC below 1 x 10^9/L. If the ANC remains below 1 x 10^9/L for more than 3 weeks, do not restart vinorelbine. If fever develops while the ANC is over 1.5 x 10^9/L or therapy is delayed 2 weeks, then use 22.5 mg/m^2 or 11.25 mg/m^2 for an ANC between 1 - 1.499 x 10^9/L.
E) Vinorelbine is a vesicant.

IV. TOXICITY
A) Neutropenia is the dose limiting side effects. Onset on day 7-10 and recovery by day 14-24. Anemia is modest and platelets are spared.
B) Peripheral neuropathy occurs in fewer patients than with vincristine. It occurs in 20% of patients and is rarely severe. It appears to be reversible. Cisplatin does not exacerbate the problem but prior paclitaxel will increase the risk.
C) Injection site reactions occur in 26% of patients and include erythema, pain, vein discoloration, and phlebitis. Short infusion with flushing afterwards will minimize the reaction. Vinorelbine is a vesicant as well.
D) Chemical hepatitis.
E) Vasospastic angina.
F) GI toxicity is mild. Constipation 30%, ileus 3%, diarrhea 8%.
G) Alopecia is uncommon.

V. CLINICAL MONITORING
A) Be sure IV site is usable.
B) Check CBC and bilirubin prior to therapy.
C) Check neurological exam prior to therapy.