Chapter 2

The Vinca Alkaloids

Nicole Coufal and Lauge Farnaes

2.1 Introduction

The periwinkle plant, *Cantharanthus roseus* G. Don (*Vinca rosea* Linn.) is endemic to the island of Madagascar, and has long been ascribed a wide assortment of medicinal properties ranging from the treatment of diabetes to wound healing. Of the over fifty alkaloids present in minute quantities within the plant, only two (vincristine and vinblastine) have been isolated, synthesized, and are widely used as chemotherapeutic agents [1, 2]. The antitumor activity of the vinca alkaloids was identified by two independent groups both investigating extracts of *Vinca rosea* for hypoglycemic activity in the late 1950s [2, 3]. Numerous other natural alkaloids were also investigated but not pursued due to severe toxicity [4]. Now the vinca alkaloids have become part of the standard of care for more than 30 years. A number of semisynthetic derivates have since been identified and tested. Two of these, vindesine and vinorelbine, are currently used in clinical practice. A third, vinflunine, is presently in phase III clinical trials [5, 6].

These compounds are commonly administered as sulfate salts to enhance solubility and increase stability. All members of this family of molecules enact their cytotoxic activity primarily by binding to tubulin and inhibiting polymerization or extension of microtubules. Microtubules are crucial for a wide range of cellular activities, including mitotic spindles formation necessary for cell division. The naturally occurring vinca alkaloids have been used in the treatment of a wide range of malignancies, most prominently hematological cancers such as leukemia and lymphoma, but also testicular cancer. The semi-synthetics have exhibited clinical activity against lung, ovarian, and breast malignancies.

2.2 Chemistry

The vinca alkaloids are bulky molecules with closely related structures (Fig. 2.1), containing both an indole nucleus (catharanthine portion) and a dihydroindole nucleus (vindoline portion) connected by a carbon–carbon ring with variable substituents attachment to the rings. Vincristine differs from vinblastine, vindesine, and vinorelbine as it has an acetaldehyde group at the nitrogen atom at position one (see vincristine in Fig. 2.1 for numbering) in the vindoline nucleus instead of a methyl group. Vincristine, vinblastine, and vinorelbine all have a methyl ester moiety attached to carbon 3 in the vindoline nucleus while vindesine has an amide attached at this same site. Vincristine, vinblastine, and vinorelbine are all acetylated at carbon 4 while vindesine has a hydroxyl group. Vinorelbine also has a different structure in the catharanthine portion of the molecule with the 11-membered ring being replaced with a 10-membered ring by the elimination of carbon 7′.

2.3 Mechanism of Action

The vinca alkaloids interact with tubulin thereby disrupting the mitotic spindle apparatus [7–9]. Tubulin is usually present as a heterodimer of α-tubulin and

N. Coufal (✉)
UCSD Department of Medicine, 9500 Gilman Drive, La Jolla, CA 92093, USA
e-mail: ncoufal@ucsd.edu

B.R. Minev (ed.), *Cancer Management in Man: Chemotherapy, Biological Therapy, Hyperthermia and Supporting Measures*, Cancer Growth and Progression 13,
DOI 10.1007/978-90-481-9704-0_2, © Springer Science+Business Media B.V. 2011

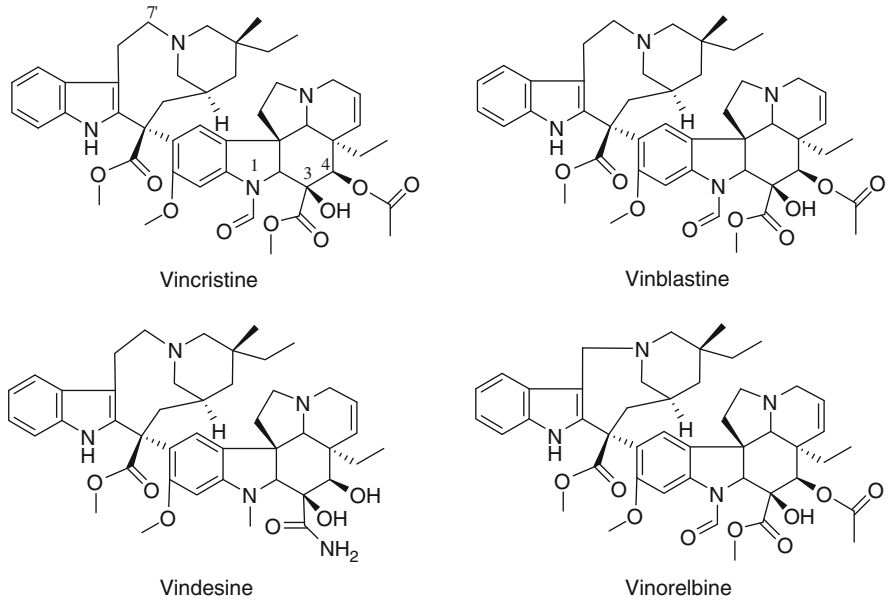

Fig. 2.1 The structure of the vinca alkaloids

β-tubulin each with a molecular weight of 55 kDa. The heterodimers polymerize to form microtubules which are involved in mitosis and meiosis through the formation of the spindle apparatus which separates the chromosomes. In addition microtubules are involved in cell shape, axonal transport, and secretion [10]. The biological function of microtubules is determined largely by their polymerization dynamics [11]. The two main types of dynamic behavior are "dynamic instability" and "treadmilling." The assembly and disassembly of the microtubule polymers are regulated by the binding of tubulin and guanosine 5-triphoshpate (GTP) [12]. All microtubules have a plus end of the microtubule that polymerizes faster and thereby grows faster than the opposing minus end. Dynamic instability is characterized by changes in the length of the microtubule structure, primarily at the plus end whereas treadmilling is characterized by the movement of cellular components along a tubule that is maintained at constant length, with equal addition at the minus end and subtraction at the plus end. It has been suggested that treadmilling might be particularly important in mitosis [13]. In mitosis the microtubules form the spindle apparatus which aligns the chromosomes along the metaphase plate and then pulls the chromosomes apart during the mitotic process.

All the vinca alkaloids bind to tubulin with high affinity and inhibit further polymerization. Since microtubules are in a constant dynamic state of polymerization and depolymerization the inhibition of polymerization by the vinca alkaloids functions to create a state of net depolymerization. The interaction of the vinca alkaloids with the microtubules of the spindle apparatus disrupts the spindle apparatus and leads to metaphase arrest. Vinorelbine, vincristine, and vinblastine have all been shown to possess roughly equal tubulin binding constants [8] and cause metaphase block at roughly the same concentrations. It has been suggested that the differences in the relative potencies of the vinca alkaloids may not be due to their binding efficiencies but rather to differences in their intracellular retention times or the stability of the drug-tubulin complexes [14]. In addition, vincristine is a much more potent inhibitor of axonal microtubule formation [15].

While the disruption of the mitotic process is the key feature of the vinca alkaloids the final effect of this metaphase arrest is the death of the cell through activation of apoptotic pathways [16, 17]. In vitro experiments with these agents have shown that exposure can lead to apoptosis through both p53-dependent and p53-independent pathways [18–20]. Tumor cells that have been exposed to the agents show characteristic morphological and molecular changes that are

associated with the induction of apoptosis in a dose and time dependent fashion. Since the drugs attempt to induce apoptosis by halting the cell in mitosis, cytotoxicity is strongly dependent on the duration of exposure.

A number of other cellular effects beyond microtubule inhibition have also been reported for the vinca alkaloids. These include inhibition of amino acid metabolism [21], calmodulin-dependent Ca^{2+} ATPase activity [22], nucleic acid synthesis [4]. In order to achieve these other effects though the concentrations of the drugs had to be at much higher levels than are achieved in vivo.

2.4 Clinical Use

The vinca alkaloids are broad acting mitotic inhibitors used in the treatment of numerous malignancies [23]. They have been used for both curative and palliative aims in the treatment of a variety of tumors, most often Hodgkin's disease, acute lymphocytic leukaemia, testicular cancer, breast carcinoma, ovarian cancer, and non-small-cell lung cancer (NSCLC). Other malignancies treated with vinca alkaloids include Wilms' tumor, Ewing's sarcoma, neuroblastomas, hepatoblastoma, and rhabdomyosarcoma.

Vincristine is part of a front-line therapy for the treatment of acute lymphocytic leukaemia. It is also commonly used in pediatric oncology owing to the higher level of sensitivity of pediatric malignancies and the better tolerance of therapeutic doses in children. Vincristine is also a standard treatment for non Hodgkin's lymphoma as part of the chemotherapy regimen CHOP (Cytoxan, Hydroxyrubicin (Adriamycin), Oncovin (Vincristine), Prednisone) [24] and as a treatment of Hodgkin's lymphoma as part of MOPP or COPP. Vincristine is also generally used in the treatment of multiple myeloma as a bolus or daily infusion in combination with doxorubicin and dexamethasone [25]. Vinblastine is used in combination with other agents as a front-line therapy for the treatment of Hodgkin's disease and testicular cancer. It is also approved for use as a single agent or in combination with cisplatin for the treatment of NSCLC and advanced breast cancer [26, 27]. Vindesine is used in combination with other agents, such as mytomycin C and/or platinating agents in the treatment of NSCLC [28]. Vinorelbine is the only vinca which can be administered orally, and resistance to vinorelbine develops more slowly and is less cross-resistant with resistance to vincristine and vinblastine. Vinflunine is currently being investigated for use in the treatment of metastatic breast cancer and NSCLC trials [5, 6].

The vinca alkaloids are routinely administered by direct intravenous injection. They are extreme vesicants (see Section 2.8) so are often administered as a rapid bolus. Vinorelbine can be administered orally. The single dose cap for vincristine is 2.0 (mg/m^2) due to substantial neurotoxicity reported at higher doses. However, significant interpatient variability exist, and some patients can tolerate much higher doses with limited toxicity [29, 30]. For vinblastine, initial dose recommendations are 2.5 and 3.7 mg/m^2 for children and adults, respectively, with gradual dose escalation based on hematologic tolerance. Vinesine has been evaluated for weekly and biweekly administrations, and is most commonly administered at 2–4 mg/m^2 every 7–14 days [27]. Additionally, prolonged infusion schedules have been evaluated to increase the critical threshold concentration of vincristine, vinblastine, and vindesine, and all indicate an increased dose can be administered safely without major toxicity for 1–2 days (vindesine) or up to 5 days (vincristine) [27]. However, there is little evidence that prolonged infusions are more effective than bolus schedules. Vinorelbine is most commonly administered at a dose of 30 mg/m^2 weekly or biweekly. It can be administered as a slow infusion or bolus, although evidence indicates decreased local venous toxicity with a bolus [31].

2.5 Mechanisms of Resistance

Resistance to the vinca alkaloids develops rapidly and can occur through alterations in numerous cell pathways.

For chemotherapeutic agents, resistance is commonly due to decreased drug accumulation and retention within target tumor cells. The most widely documented mechanism of vinca alkaloid efflux is by members of the ATP-binding cassette (ABC) transporter family, a huge gene family of transmembrane transporters which efflux large endobiotic and xenobiotic compounds from cells in an ATP dependent fashion. Resistance via multidrug resistance channels

(MDR) can be innate or acquired. These transporters not only confer resistance to the vinca alkaloids, but also to a variety of other well known pharmacologic agents such as taxanes, anthracyclines, epipodophyllotoxins, dactinomycin and colchicine [32]. The two most investigated members of this family in regards to vinca alkaloid resistance are the permeability glycoprotein (P-gp)/MDR1 endcoded gene product (ABC subfamily B1;ABCB1) and the multidrug resistance protein MRP (ABC subfamily C2; ABCB1) [33–37]. Although these two transport systems have the same end result, they appear to utilize slightly different mechanisms. For instance, P-gp vesicles have been shown to directly transport vinca alkaloids, whereas MRP vesicles transport in a glutathione dependent fashion [34].

MDR1 is a 170-kD P-gp transmembrane pump that regulates efflux of large amphipathic hyrdophic substances in an energy dependent fashion. Drug resistance is proportional to the amount of channel present in the cell membrane [36]. Innate resistance is offered by tissues which constitutively express a high amount of the channel, such as endothelium and epithelial tissue, especially renal epithelium and colonic endothelium [38]. This channel is highly expressed in tumors arising from constitutively expressing tissues (kidney and colon cancer). Secondarily tumors can overexpress MDR1 or related ABC transporters as a result of treatment with vinca alkaloids, a phenomenon which has been observed in post-treatment leukemia, lymphoma, and multiple myeloma. MRP is a 190-kD transmembrane protein with a 15% homology to MDR1 which has been shown to mediate vinca alkaloid resistance as well as resistance to other chemotherapeutic agents such as methotrexate [32, 39–41]. Although many other ABC transporters have been characterized and implicated in vinca alkaloid resistance, their role is even less apparent than that of MDR1 and MRP.

One important feature of MDR1 and MRP resistance is that is reversible in specific conditions, such as after treatment with calcium channel blockers, detergents, progesterone or estrogenic antagonists, antibiotics, antihypertensives, antimalarials, antiarrhythmics, and immunosuppressives [32]. All of these agents bind directly to the channel and inhibit efflux, thereby increasing intracellular concentrations of chemotherapeutic agents. To date the usefulness of this observation has been limited as these agents also act to enhance drug uptake into normal cells, thereby decreasing biliary elimination and decreasing drug clearance, ultimately lead to enhanced toxicity [42–44]. In addition, MDR1 has been shown to respond to environmental stress by producing multiple alternative proteins, which could explain the unsatisfactory outcomes from pharmacologic modulations efforts thus far [32].

Other mechanisms of resistance to the vinca alkaloids have also been identified, although primarily in preclinical models. Each of these represents a different modification in the mechanism of vinca alkaloid action or of downstream signaling to allow the tumor cell to escape programmed cell death. For instance, changes in tubulin expression or tubulin binding [45] can lead to resistance. Resistant tumors have been found to contain mutations which lead to amino acid substitutions or posttranslational modifications such as acetylation or phosphorylation and thereby change the structure of tubulin [46, 47]. Although the mechanism of resistance in these cases is not entirely clear, it is thought to be as a result of hyper-stabilization of tubulin rather than a change in the drug binding affinity of the vinca alkaloids [48]. In addition, changes in heat shock response [49] or alterations in apoptotic signaling allowing cells to escape apoptosis [50, 51]. Typically apoptosis in response to the vinca alkaloids is initiated through a lengthy set of signaling pathways comprising c-jun and stress-activated protein kinase activation [19]. Therefore, overexpression of anti-apoptotic genes such as Bcl-2 and Bcl-XL has been shown to afford resistance to a wide assortment of chemotherapeutic agents including vincristine and vinblastine [52, 53].

2.6 Pharmacokinetics

Pharmacokinetic data on the vinca alkaloids has been hampered by a lack of sensitive, specific, and reliable detection methods in the past. Since the vinca alkaloids are given in such minute amounts it had been necessary to trace them with radioactively labeled drugs. This was a difficult process as the vinca alkaloids can be somewhat unstable and rapidly form degradation products which can be separated by high-pressure liquid chromatography (HPLC) [54]. In an effort to further understand the distribution of the vinca alkaloid, radioimmuno assay and enzyme-linked immunosorbent assay (ELISA) have been developed that can observe the vinca alkaloids in the picomolar

concentraton range [27]. These assays were originally performed with polyclonal antisera which were hampered by reactions with possible metabolites but in the interim monoclonal antibodies were raised which have allowed for more precise tracking of the vinca alkaloids in vivo.

The vinca alkaloids are most commonly given intravenously by bolus injection or brief infusion and their pharmacokinetic profile most closely fits a three compartment model [27]. Characteristics of the vinca alkaloids include large volumes of distribution, high clearance rates, long terminal half lives ($T_{1/2}$), significant hepatic metabolism, and biliary/fecal metabolism. With a normal adult dose peak plasma concentrations of 100–500 nmol are maintained for only a few minutes with concentrations of 1–2 nmol persisting for longer durations [55, 56]. There can be a significant variation in the pharmacokinetics of these drugs in different patients. This may be due to variations in protein or tissue binding, hepatic metabolism and/or biliary clearance [57]. Although prolonged infusion schedules may help to avoid excessively toxic peak concentration levels and increase the duration of drug exposure, there is no evidence that prolonged infusion schedules are more effective than bolus schedules [58].

Vincristine, vinblastine, and vindesine are only given by an intravenous route but vinorelbine can be given both by intravenous and oral routes. Oral absorption of vinorelbine is rapid with maximal drug concentrations achieved in 1–2 h with an absolute bioavailability of approximately 27% with a range of 10–60% [58] when given in soft gelatin capsules. The oral clearance of vinorelbine approaches hepatic flow (0.8 L/H/Kg) suggesting a significant first-pass effect. Due to the large first pass effect, oral doses may need to be up to three times larger than intravenous doses to achieve the same effect. In addition the bioavailability of oral vinorelbine may be lowered slightly by food [59] (Table 2.2).

The vinca alkaloids all bind strongly to plasma proteins including albumin, lipoproteins, and α1-acid glycoprotein [61]. The primary binding protein for the vinca alkaloids is α1-acid glycoprotein with an approximately 10 fold higher affinity for these compounds than for albumin [62, 63]. At drug concentrations similar to those achieved in vivo protein binding of vincristine and vinblastine is 99% suggesting that the total binding sights for the vinca alkaloids are saturatable [64]. In addition to the binding of vinca alkaloids to serum proteins the vinca alkaloids also rapidly bind to platelets and lymphocytes after intravenous infusion [61, 65]. Platelet bound drug accounts for approximately 80% of the blood bound drug. The distribution of the drug into platelets and lymphocytes is ½ h for vinorelbine, 1 h for vinblastine, and 3 h for vincristine [61, 65]. Since the binding of the drug to platelets is a reversible process and the release of vincristine is much slower than it is vinblastine or vinorelbine this may explain the differences in their respective $T_{1/2}$ (see Table 2.1).

Table 2.1 Properties of the vinca alkaloids

	Vincristine	Vinblastine	Vindesine	Vinorelbine
Mechanism of action	Low concentrations inhibit changes in microtubule length (treadmilling and dynamic instability) whereas high concentrations inhibit polymerization of tubulin			
Standard Dose (mg/m^2)	1–1.4 every 3 weeks	6–8 every week	3–4 every 1–2 weeks	15–30 every 1–2 weeks
Route of administration	Intravenous	Intravenous	Intravenous	Intravenous, oral
Metabolism	Predominantly P450 IIIA	Predominantly P450 IIIA	Predominantly P450 IIIA	Predominantly P450 IIIA
Elimination	Biliary/Fecal	Biliary/Fecal	Biliary/Fecal	Biliary/Fecal
Terminal half-life (h) ($T_{1/2}$)	95 (range 19–155)	25 (range 7–47)	24 (range 12–42)	33 (range 14–44)
Principal toxicity	Peripheral Neuropathy	Neutropenia	Neutropenia	Neutropenia

Table 2.2 Disposition of vinca alkaloids by bolus injection in patients with normal organ function [60]

	Volume of distribution (l/kg)	Elimination half-life (h)	Clearance (l/h/kg)	Fecal Clearance (%)	Renal Clearance (%)
Vincristine	7.2 (3.1–11.0)	45.1 (8.2–144)	0.16 (0.1–0.3)	69	4–13.5
Vinblastine	24.7 (17.3–35.1)	25.6 (19.6–29.2)	0.79 (0.7–0.9)	25–41	5.5–34
Vindesine	8.6 (6.8–10.5)	23.6 (19.0–34.8)	0.22 (0.1–0.3)	ND	4–19
Vinorelbine	54.3 (44.7–75.6)	41.2 (31.2–62.4)	0.95 (0.8–1.3)	40–58	3.3–24.6

Animal studies using radiolabeled drugs show that, following intravenous administration the vinca alkaloids are rapidly and widely distributed throughout the body [66–70]. After treatment with radiolabeled vincristine, vinblastine, or vindesine radioactivity is concentrated in the spleen, liver, kidney, lymph nodes, and thymus. Moderate levels are found in lungs, heart, and skeletal muscle. Brain and fat contain low levels. Not all of these studies were able to clearly distinguish between drug and degradation products. Vinorelbine also accumulates in the spleen, liver, kidney, and to very high levels in the lungs. Tracing the distribution of radioactively labeled vinorelbine in patients shows that the concentration of drug in the lungs may be up to 300 times greater than that in the serum and 3.4–13.8 fold higher than the lung concentration that is achieved by vincristine or vindesine [71]. This higher concentration of vinorelbine in the lungs is a primary reason for its preferential use in the treatment of non-small cell lung cancer. In addition, vinblastine is more actively sequestered in tissue than is vincristine as demonstrated by a retention of 73% of radioactivity in the body six days post-treatment [72].

The vinca alkaloids have poor penetration into the central nervous system (CNS). Although these drugs have a high lipophilicity their extensive lymphocyte, platelet and protein binding prevents them from penetrating the blood brain barrier (BBB). Additionally, since the vinca alkaloids are substrates for permeability glycoprotein (P-gp) and this protein is an active part of the blood brain barrier, any vinca alkaloid that does pentrate the BBB is actively removed. It has been found that mice that lack P-gp have a 22 fold higher accumulation of the vinca alkaloids when compared to mice that express wild-type P-gp [73].

Accumulation and uptake of the vinca alkaloids shows a direct correlation to their respective lipophilicities. Since vinorelbine is the most lipophilic of the vinca alkaloids it also exhibits the most liver uptake of the vinca alkaloids [74].

In vitro experiments using freshly isolated hepatocytes have shown that vincristine, vinblastine, vindesine, and vinorelbine are almost totally converted to water soluble metabolites which are then excreted into the extracellular fluid [56, 70, 75]. The nature of the metabolites that have been identified so far suggest that the vinca alkaloids are metabolized by the hepatic cytochrome P-450 mixed function oxidase CYP3A [26, 54, 56, 76–78]. The importance of CYP3A in the metabolism of the drug is the observation of increased clearance of the drug when used in conjunction with drugs that induce CYP3A, such as phenytoin and carbamazepine and the incidence of increased toxicity with CYP3A inhibitors such as itraconazole [77, 79]. It also appears that the individual vinca alkaloids inhibit the biotransformation of one another indicating a common metabolic pathway that is saturable. Although few of the metabolites of the vinca alkaloids have been actively studied, low levels of deacetylated vinblastine and vinorelbine have been detected in the feces, urine and tissues of animals [80, 81]. In human patients only deacetylated vinorelbine has been observed in a very small amount in the urine. It appears though that the deacetylated metabolite of vinorelbine is equipotent to the parent compound [81].

The vinca alkaloids are primarily eliminated by the hepatobiliary system. There is some variation in the percentages of metabolites that are excreted in the feces or the urine between the various vinca alkaloids but roughly between 33 and 80% excreted in the feces with up to 40% consisting of metabolites and 12 and 30% excreted in the urine most of which is unmetabolized [26, 56, 67, 69, 72, 76, 81–84]. Vincristine is rapidly excreted into the bile with an initial bile to plasma concentration ratio of 100:1 which declines to 20:1 by 72 h post treatment [67]. As a result of compounds being eliminated through the hepatobiliary system extra care must be exercised in patients with compromised liver function such as liver metastases or cirrhosis of the liver.

2.7 Doses and Schedules

The vinca alkaloids are most commonly administered by direct intravenous injection. Only experienced oncology personnel should administer these agents as extravasation causes severe soft tissue injury.

2.7.1 Vincristine

Vincristine may be given to pediatric patients weighing less than 10 kg (body surface area <1 m^2) at 0.05–0.065 mg/kg weekly. In children weighing more than 10 kg (body surface area ≥ 1 m^2) a bolus injection dose

of 1.5–2.0 mg/m^2 may be given weekly. For adults the common dose is 1.4 mg/m^2 weekly. There have been efforts to create a prolonged infusion scheme as a result of some evidence that the duration of exposure above a critical concentration is important for cytotoxicity [27, 85]. A restriction of the absolute single dose of 2.0 mg/m^2 has been adopted due to early reports of substantial neurotoxicity at higher doses. There is some evidence now that this cap should be reconsidered [86]. The setting of a cap for the maximum dose is further complicated by the large amount of interpatient variability in the tolerance of and metabolism of these compounds. Vincristine dosage modification should be based on the appearance of toxicity such as the appearance of peripheral or autonomic neuropathy [87]. The dosage should not be reduced for mild peripheral neuropathy especially if it is being used in a curative setting. If there are more serious toxic effects associated with serious neurotoxicity such as sensory changes, motor or cranial nerve changes or ileus then the dosage should be modified until there is an adequate reduction of symptoms of toxicity. In palliative settings it may be advisable to reduce dosage or select an alternative agent for moderate toxicity. Due to the hepatobiliary elimination of vincristine a 50% dose reduction is indicated for patients with plasma total bilirubin levels of 1.5–3.0 mg/dl and a 75% dose reduction for patients with a serum total bilirubin >3.0 mg/ml. There is no dosage reduction indicated for renal dysfunction [88, 89].

2.7.2 Vinblastine

Vinblastine may be given to pediatric patients on a weekly schedule starting at 2.5 mg/m^2 followed by dose escalation of 1.25 mg/m^2 each week based on hematological tolerance of the drug. It is not recommended to administer a dose higher than 12.5 mg in pediatric patients although most patients have myelosuppression before this dose level is reached. Adults may be given a weekly schedule starting at 3.7 mg/m^2 followed by dose escalation of 1.8 mg/m^2 each week based on hematological tolerance of the drug. It is not recommended to use a dose higher than 18.5 mg in adult patients although most patients have myelosuppression at submaximal doses regardless. Vinblastine is also commonly used as a bolus injection of 6 mg/m^2 in cyclic combination chemotherapy regimens. Because leukopenia occurring with the administration of vinblastine can vary widely with identical doses, vinblastine should not be administered more than once per week. Although there are no specific guidelines for dose reduction in patients with compromised liver function it would most likely be necessary to significantly reduce the dosage of the drugs due to the hepatic role in the clearing of these drugs.

2.7.3 Vindesine

Vindesine is most commonly given as an intravenous bolus of 2–4 mg/m^2 weekly to biweekly which is associated with antitumor activity and a tolerable toxicity prolfile [27]. Intermittent or continuous schedules usually infuse 1–2 mg/m^2 per day for 1–2 days or 1.2 mg/m^2 for 5 days every 3–4 weeks [27, 56]. As with the other vinca alkaloids a dose reduction is warranted if the patient has hepatic dysfunction.

2.7.4 Vinorelbine

Vinorelbine is commonly given intravenously at dose of 30 mg/m^2 as an injection using the sidearm port of a running infusion. Alternatively vinorelbine may be given as a slow bolus injection followed by flushing with 0.9% sodium chloride or a short infusion over 20 min. It appears that the shorter infusions are associated with a decrease in local venous toxicity [31]. Patients with hepatic dysfunction should be given a lower dose [90]. Dosage reductions for hepatic dysfunction include a 50% reduction in patients with serum total bilirubin between 1.5 and 3.0 mg/dl and a 75% reduction in patients with serum total bilirubin >3.0 mg/dl. As with the other vinca alkaoids dosage reductions are not indicated in patients with renal insufficiency.

2.8 Toxicity

Despite the structural and pharmacologic resemblance between vinca alkaloid family members, a broad range of adverse reactions have been noted, and

there are striking differences in the severity and incidence of adverse reactions for each. There is no precise explanation for these side-effects, however the affinity for tubulin and the cellular uptake rate is likely the culprit. The predominant toxicity for vincristine is neurotoxicity, whereas myelosuppresion is most frequent with vinblastine, vinesine, and vinorelbine. However, peripheral neurotoxicity and myelosuppresion can be associated with any vinca alkaloid as a result of prolonged treatment, unintentional high-dose treatment, or in highly susceptible patients (e.g., individuals with hepatic dysfunction or the elderly).

The ability of the vinca alkaloids to bind tightly to microtubules present in peripheral nerves, which are essential for axonal transport and secretory functions makes neurotoxicity unavoidable. Axonal degeneration and decreased axonal transport result, and can be measured as diminished amplitude of sensory and motor nerve action potentials and prolonged distal latencies [26, 91]. Despite being highly lipophilic, the large size and significant platelet and protein binding activity of these agents prevents them from crossing the blood-brain barrier. Additionally, MDR1 is highly expressed in brain capillary endothelium, resulting in drug efflux [92]. As a result, neural toxicity is primarily as a result of peripheral nerve damage, and central nervous system toxicity is rare [2]. There are numerous reports of seizures after administration, but due to low CNS penetration, are unlikely to be directly due to vinca alkaloid administration. They are more likely a result of intracranial metastasis, infection, or as a result of hyponatremia secondary to inappropriate antidiuretic hormone secretion which can be caused by vincristine [93].

Neurotoxicity as a result of vinca alkaloid treatment is characterized by peripheral, symmetric mixed sensory, motor, and autonomic polyneuropathy [26, 94, 95]. Neurotoxicity occurs as a well-documented progression in most patients, usually beginning with asymptomatic Achilles tendon reflex loss [93], followed by paresthesias in the hands and feet. This is followed by neuritic pain, and can progress to foot drop, wrist drop, muscle pain, weakness, ataxia, and paralysis. Deficits are symmetrical and may persist for weeks or months after therapy is discontinued [93]. Rarely the cranial nerves are affected, resulting in dipolopia, hoarseness, and facial palsies. Severe jaw pain has been reported shortly after administration, but does not usually persist [93]. Autonomic neuropathies are common, ranging from constipation, bloating, and abdominal pain to paralytic ileus in the more severe cases. Paralytic ileus, intestinal necrosis, and perforation have lead to several deaths as a consequence of vinca alkaloid treatment [93, 96]. Gastrointestinal effects are generally most severe with vincristine [2, 58]. Autonomic neurotoxicity secondary to vincristine may produce bladder atony and resulting polyuria, dysuria, and urinary retention [97]. Cardiovascular autonomic neurotoxicities have also been reported, most frequently hypertension and hypotension, but also rarely cardiac ischemia and massive myocardial infarctions when vinca alkaloids are combined with cisplatin and bleomycin [98, 99]. Frequently mild autonomic neuropathies precede more severe peripheral neuropathies.

Attempts to reverse or prevent neurotoxicity have been largely unsuccessful, as a result supportive care and dose adjustments are the primary treatments [94, 100]. There has been limited success with folinic acid (not folic acid) which has been shown to protect against an otherwise lethal dose of vincristine in animal models, and used in several overdose patients [88, 89]. Also shown to have some efficacy is gluatmic acid and a mixture of gangliosides to reduce neurotoxicity [101, 102]. Patients should be routinely treated with dietary bulk, stool softeners, and laxatives to prevent severe constipation.

All the vinca alkaloids have been shown to act directly on the hypothalamus, posterior pituitary, or neurohypophyseal tract (where the blood-brain barrier is the least robust) and can cause syndrome of inappropriate antidiuretic hormone secretion (SIADH). Patients who are already receiving extensive hydration are particularly susceptible to hyponatremia as a result of SIADH and can result in generalized seizures [2, 27]. Usually elevated plasma ADH levels return to normal within two to three days. Hyponatremia should be treated with fluid restriction, as SIADH would be treated from other causes.

Bone marrow suppression is a common side effect of the vinca alkaloids. Leukopenia is common, peaking 5–10 days after drug administration. Extent and duration of leucopenia is dose dependent. White cell count returns to normal within 1–2 weeks, and myelosuppression is not typically cumulative. Thrombocytopenia and anemia are less common and severe, unless used in combination with radiation or

other agents. Leukopenia is least pronounced with vincristine, and is therefore the agent of choice if bone marrow suppression is dose-limiting.

Vincristine, vinblastine, and vindesine are strong vesicants, and extreme caution should be taken in their administration to avert leakage into surrounding tissues. They should never be administered intramuscularly, subcutaneously, or intraperitoneally. Inadvertent intrathecal injection, which has occurred in clinical accidents, induces severe myeloencephalopathy including ascending motor and sensory neuropathies and rapid death [103]. It is recommended that these agents be administered as a bolus whenever possible to minimize risk of extravasation. Injection site reactions include erythema, pain, and venous discoloration. There is a risk of phlebitis if veins are not flushed after administration. If extravasation is suspected, treatment should cease, and aspiration of any residual drug attempted [104]. Extravasation has been successfully treated with corticosteroids to limit tissue damage [104]. Immediate surgical consultation to consider early debridement should be considered.

Dosage modifications should be based on toxicity, although mild toxicity is acceptable in a curative setting. Severe toxicities, such as ileus and sensory, motor, and cranial nerve deficits indicate a need for dose modification. In palliative situations, modifying doses or increasing dosing intervals may be justified even with moderate neurotoxicity. Due to their hepatic clearance, vinca alkaloid dose modifications should be considered for patients with low hepatic function [100]. A 75% dose reduction is recommended for patients with serum total bilirubin levels < 3.0 mg/dL, and a 50% dose reduction for patients with plasma total bilirubin of 1.5–3.0 mg/dL [88, 89]. Dose reductions is not indicated for patients with renal dysfunction [88, 89]. Lastly, dose reductions should be considered with elderly patients, who often exhibit reduced hepatic function.

2.9 Drug Interactions

Pharmacokinetic interactions have not been extensively studied. Those pharmaceuticals which are known to interact with the vinca alkaloids are primarily those which utilize the same elimination pathway, liver cytochrome P450 3A (CYP3A) metabolism. This includes drugs such as quinine, cyclosporine, and nifedipine which are also substrates for CYP3A, and have been shown to inhibit vinca alkaloid metabolism in vitro [75]. Nifedipine has been shown to decrease patient's plasma clearance of vincristine by 69% [105]. Administration of vinca alkaloids in combination with drugs which actively inhibit CYP3A, such as erythromycin and itraconazole, can lead to severe toxicity.

There are several medications where administration concomitantly with vinca alkaloids can lead to excessive toxicity. For instance, the use of mitomycin C in combination with vinca alkaloids is associated with pulmonary toxicity [106, 107]. These reactions are usually either acute bronchospasm or subacute reversible cough and dyspnea 1 h after treatment. Furthermore, treatment with vinblastine in combination with either erythromycin or cyclopsorin leads to greater than predicted vincristine toxicity [108, 109]. Similarly, vincristine associated toxicity is much higher with concomitant etoposide treatment (another substrate for CYP3A) [110]. Lastly, the large degree of variability within and between individuals in vincristine pharamcokinetics has been ascribed to unpredictable CYP3A induction secondary to corticosteroid therapy [111].

Pharmaceuticals which upregulate liver enzymes may increase vinca alkaloid metabolism (e.g., phenytoin and phenobarbitol) and decrease their efficacy [112, 113]. Conversely, treatment with vinca alkaloids has precipitated seizures associated with subtherapeutic plasma phenytoin concentrations, likely as a result of CYP3A induction [86, 114]. Reduced phenytoin levels have been documented 24 h–10 days post treatment with vinblastine and vincristine.

References

1. Cutts JH, Beer CT, Noble RL (1960) Biological properties of Vincaleukoblastine, an alkaloid in *Vinca rosea* Linn, with reference to its antitumor action. Cancer Res 20:1023–1031
2. Johnson IS, Armstrong JG, Gorman M, Burnett JP Jr (1963) The Vinca alkaloids: a new class of oncolytic agents. Cancer Res 23:1390–1427
3. Beer CT, Gallagher TF (1955) Excretion of estrogen metabolites by humans. I. The fate of small doses of estrone and estradiol-17beta. J Biol Chem 214(1):335–349
4. Creasey W (1975) Vinca alkaloids and colchicine. In: Sartorelli AC, Johns DG (eds) Antineoplastic and

immunosuppressive agents part II, vol 38. Springer, Berlin, pp 232–256
5. Bennouna J, Breton JL, Tourani JM, Ottensmeier C, O'Brien M, Kosmidis P et al (2006) Vinflunine – an active chemotherapy for treatment of advanced non-small-cell lung cancer previously treated with a platinum-based regimen: results of a phase II study. Br J Cancer 94(10):1383–1388
6. Campone M, Cortes-Funes H, Vorobiof D, Martin M, Slabber CF, Ciruelos E et al (2006) Vinflunine: a new active drug for second-line treatment of advanced breast cancer. Results of a phase II and pharmacokinetic study in patients progressing after first-line anthracycline/taxane-based chemotherapy. Br J Cancer 95(9):1161–1166
7. Na GC, Timasheff SN (1982) In vitro vinblastine-induced tubulin paracrystals. J Biol Chem 257(17): 10387–10391
8. Lobert S, Vulevic B, Correia JJ (1996) Interaction of vinca alkaloids with tubulin: a comparison of vinblastine, vincristine, and vinorelbine. Biochemistry 35(21):6806–6814
9. Himes RH (1991) Interactions of the catharanthus (Vinca) alkaloids with tubulin and microtubules. Pharmacol Ther 51(2):257–267
10. Luduena RF, Shooter EM, Wilson L (1977) Structure of the tubulin dimer. J Biol Chem 252(20):7006–7014
11. Waterman-Storer CM, Salmon ED (1997) Microtubule dynamics: treadmilling comes around again. Curr Biol 7(6):R369–R372
12. Mitchison TJ (1993) Localization of an exchangeable GTP binding site at the plus end of microtubules. Science 261(5124):1044–1047
13. Chen W, Zhang D (2004) Kinetochore fibre dynamics outside the context of the spindle during anaphase. Nat Cell Biol 6(3):227–231
14. Singer WD, Himes RH (1992) Cellular uptake and tubulin binding properties of four Vinca alkaloids. Biochem Pharmacol 43(3):545–551
15. Binet S, Chaineau E, Fellous A, Lataste H, Krikorian A, Couzinier JP et al (1990) Immunofluorescence study of the action of navelbine, vincristine and vinblastine on mitotic and axonal microtubules. Int J Cancer 46(2):262–266
16. Tsukidate K, Yamamoto K, Snyder JW, Farber JL (1993) Microtubule antagonists activate programmed cell death (apoptosis) in cultured rat hepatocytes. Am J Pathol 143(3):918–925
17. Harmon BV, Takano YS, Winterford CM, Potten CS (1992) Cell death induced by vincristine in the intestinal crypts of mice and in a human Burkitt's lymphoma cell line. Cell Prolif 25(6):523–536
18. Li G, Tang L, Zhou X, Tron V, Ho V (1998) Chemotherapy-induced apoptosis in melanoma cells is p53 dependent. Melanoma Res 8(1):17–23
19. Yu K, Ravera CP, Chen YN, McMahon G (1997) Regulation of Myc-dependent apoptosis by p53, c-Jun N-terminal kinases/stress-activated protein kinases, and Mdm-2. Cell Growth Differ 8(7):731–742
20. Fan S, Cherney B, Reinhold W, Rucker K, O'Connor PM (1998) Disruption of p53 function in immortalized human cells does not affect survival or apoptosis after taxol or vincristine treatment. Clin Cancer Res 4(4):1047–1054
21. Cline MJ (1968) Effect of vincristine on synthesis of ribonucleic acid and protein in leukaemic leucocytes. Br J Haematol 14(1):21–29
22. Watanabe K, West WL (1982) Calmodulin, activated cyclic nucleotide phosphodiesterase, microtubules, and vinca alkaloids. Fed Proc 41(7):2292–2299
23. Chabner BA (1992) Mitotic inhibitors. Cancer Chemother Biol Response Modif 13:69–74
24. Nachman J (1990) Therapy for childhood non-Hodgkin's lymphomas, nonlymphoblastic type. Review of recent studies and current recommendations. Am J Pediatr Hematol Oncol 12(3):359–366
25. Dimopoulos MA, Pouli A, Zervas K, Grigoraki V, Symeonidis A, Repoussis P et al (2003) Prospective randomized comparison of vincristine, doxorubicin and dexamethasone (VAD) administered as intravenous bolus injection and VAD with liposomal doxorubicin as first-line treatment in multiple myeloma. Ann Oncol 14(7):1039–1044
26. Joel S (1996) The comparative clinical pharmacology of vincristine and vindesine: does vindesine offer any advantage in clinical use? Cancer Treat Rev 21(6):513–525
27. Rowinsky EK, Donehower RC (1991) The clinical pharmacology and use of antimicrotubule agents in cancer chemotherapeutics. Pharmacol Ther 52(1):35–84
28. Dancey J, Steward WP (1995) The role of vindesine in oncology –recommendations after 10 years' experience. Anticancer Drugs 6(5):625–636
29. Costa G, Hreshchyshyn MM, Holland JF (1962) Initial clinical studies with vincristine. Cancer Chemother Rep 24:39–44
30. Peltier AC, Russell JW (2002) Recent advances in drug-induced neuropathies. Curr Opin Neurol 15(5):633–638
31. Zeffren J, Yagoda A, Kelsen D, Winn R (1984) Phase I-II trial of a 5-day continuous infusion of vinblastine sulfate. Anticancer Res 4(6):411–413
32. Cornwell MM, Tsuruo T, Gottesman MM, Pastan I (1987) ATP-binding properties of P glycoprotein from multidrug-resistant KB cells. Faseb J 1(1):51–54
33. Inaba M, Fujikura R, Sakurai Y (1981) Active efflux common to vincristine and daunorubicin in vincristine-resistant P388 leukemia. Biochem Pharmacol 30(13):1863–1865
34. Lautier D, Canitrot Y, Deeley RG, Cole SP (1996) Multidrug resistance mediated by the multidrug resistance protein (MRP) gene. Biochem Pharmacol 52(7):967–977
35. Lockhart AC, Tirona RG, Kim RB (2003) Pharmacogenetics of ATP-binding cassette transporters in cancer and chemotherapy. Mol Cancer Ther 2(7):685–698
36. Nooter K, Westerman AM, Flens MJ, Zaman GJ, Scheper RJ, van Wingerden KE et al (1995) Expression of the multidrug resistance-associated protein (MRP) gene in human cancers. Clin Cancer Res 1(11):1301–1310
37. Sikic BI, Fisher GA, Lum BL, Halsey J, Beketic-Oreskovic L, Chen G (1997) Modulation and prevention of multidrug resistance by inhibitors of P-glycoprotein. Cancer Chemother Pharmacol 40 Suppl:S13–S19
38. Greenberger LM, Williams SS, Horwitz SB (1987) Biosynthesis of heterogeneous forms of multidrug resistance-associated glycoproteins. J Biol Chem 262(28):13685–13689

39. Hipfner DR, Mao Q, Qiu W, Leslie EM, Gao M, Deeley RG et al (1999) Monoclonal antibodies that inhibit the transport function of the 190-kDa multidrug resistance protein MRP. Localization of their epitopes to the nucleotide-binding domains of the protein. J Biol Chem 274(22):15420–15426
40. Zaman GJ, Flens MJ, van Leusden MR, de Haas M, Mulder HS, Lankelma J et al (1994) The human multidrug resistance-associated protein MRP is a plasma membrane drug-efflux pump. Proc Natl Acad Sci USA 91(19):8822–8826
41. Kruh GD, Gaughan KT, Godwin A, Chan A (1995) Expression pattern of MRP in human tissues and adult solid tumor cell lines. J Natl Cancer Inst 87(16):1256–1258
42. Bertrand Y, Capdeville R, Balduck N, Philippe N (1992) Cyclosporin A used to reverse drug resistance increases vincristine neurotoxicity. Am J Hematol 40(2): 158–159
43. List AF, Kopecky KJ, Willman CL, Head DR, Persons DL, Slovak ML et al (2001) Benefit of cyclosporine modulation of drug resistance in patients with poor-risk acute myeloid leukemia: a Southwest Oncology Group study. Blood 98(12):3212–3220
44. Pinkerton CR (1996) Multidrug resistance reversal in childhood malignancies – potential for a real step forward? Eur J Cancer 32A(4):641–644
45. Geyp M, Ireland CM, Pittman SM (1996) Resistance to apoptotic cell death in a drug resistant T cell leukaemia cell line. Leukemia 10(3):447–455
46. Amos LA, Baker TS (1979) The three-dimensional structure of tubulin protofilaments. Nature 279(5714): 607–612
47. Rai SS, Wolff J (1998) Localization of critical histidyl residues required for vinblastine-induced tubulin polymerization and for microtubule assembly. J Biol Chem 273(47):31131–31137
48. Hari M, Wang Y, Veeraraghavan S, Cabral F (2003) Mutations in alpha- and beta-tubulin that stabilize microtubules and confer resistance to colcemid and vinblastine. Mol Cancer Ther 2(7):597–605
49. Lee WC, Lin KY, Chen KD, Lai YK (1992) Induction of HSP70 is associated with vincristine resistance in heat-shocked 9L rat brain tumour cells. Br J Cancer 66(4):653–659
50. Jia L, Allen PD, Macey MG, Grahn MF, Newland AC, Kelsey SM (1997) Mitochondrial electron transport chain activity, but not ATP synthesis, is required for drug-induced apoptosis in human leukaemic cells: a possible novel mechanism of regulating drug resistance. Br J Haematol 98(3):686–698
51. Srivastava RK, Srivastava AR, Korsmeyer SJ, Nesterova M, Cho-Chung YS, Longo DL (1998) Involvement of microtubules in the regulation of Bcl2 phosphorylation and apoptosis through cyclic AMP-dependent protein kinase. Mol Cell Biol 18(6):3509–3517
52. Simonian PL, Grillot DA, Nunez G (1997) Bcl-2 and Bcl-XL can differentially block chemotherapy-induced cell death. Blood 90(3):1208–1216
53. Zhang J, Alter N, Reed JC, Borner C, Obeid LM, Hannun YA (1996) Bcl-2 interrupts the ceramide-mediated pathway of cell death. Proc Natl Acad Sci USA 93(11): 5325–5328
54. Sethi VS, Thimmaiah KN (1985) Structural studies on the degradation products of vincristine dihydrogen sulfate. Cancer Res 45(11 Pt 1):5386–5389
55. Nelson RL, Dyke RW, Root MA (1980) Comparative pharmacokinetics of vindesine, vincristine and vinblastine in patients with cancer. Cancer Treat Rev 7(Suppl 1): 17–24
56. Rahmani R, Bruno R, Iliadis A, Favre R, Just S, Barbet J et al (1987) Clinical pharmacokinetics of the antitumor drug navelbine (5′-noranhydrovinblastine). Cancer Res 47(21):5796–5799
57. Beck WT, Mueller TJ, Tanzer LR (1979) Altered surface membrane glycoproteins in Vinca alkaloid-resistant human leukemic lymphoblasts. Cancer Res 39(6 Pt 1): 2070–2076
58. Rowinsky EK, Noe DA, Trump DL, Winer EP, Lucas VS, Wargin WA et al (1994) Pharmacokinetic, bioavailability, and feasibility study of oral vinorelbine in patients with solid tumors. J Clin Oncol 12(9):1754–1763
59. Bugat R, Variol P, Roche H, Fumoleau P, Robinet G, Senac I (2002) The effects of food on the pharmacokinetic profile of oral vinorelbine. Cancer Chemother Pharmacol 50(4):285–290
60. van Tellingen O, Sips JH, Beijnen JH, Bult A, Nooijen WJ (1992) Pharmacology, bio-analysis and pharmacokinetics of the vinca alkaloids and semi-synthetic derivatives (review). Anticancer Res 12(5):1699–1715
61. Urien S, Bree F, Breillout F, Bastian G, Krikorian A, Tillement JP (1993) Vinorelbine high-affinity binding to human platelets and lymphocytes: distribution in human blood. Cancer Chemother Pharmacol 32(3):231–234
62. Fitos I, Visy J, Simonyi M (1991) Binding of vinca alkaloid analogues to human serum albumin and to alpha 1-acid glycoprotein. Biochem Pharmacol 41(3): 377–383
63. Steele WH, Haughton DJ, Barber HE (1982) Binding of vinblastine to recrystallized human alpha 1-acid glycoprotein. Cancer Chemother Pharmacol 10(1):40–42
64. Steele WH, King DJ, Barber HE, Hawksworth GM, Dawson AA, Petrie JC (1983) The protein binding of vinblastine in the serum of normal subjects and patients with Hodgkin's disease. Eur J Clin Pharmacol 24(5): 683–687
65. Gout PW, Wijcik LL, Beer CT (1978) Differences between vinblastine and vincristine in distribution in the blood of rats and binding by platelets and malignant cells. Eur J Cancer 14(11):1167–1178
66. El Dareer SM, White VM, Chen FP, Mellet LB, Hill DL (1977) Distribution and metabolism of vincristine in mice, rats, dogs, and monkeys. Cancer Treat Rep 61(7):1269–1277
67. Castle MC, Margileth DA, Oliverio VT (1976) Distribution and excretion of (3H)vincristine in the rat and the dog. Cancer Res 36(10):3684–3689
68. Culp HW, Daniels WD, McMahon RE (1977) Disposition and tissue levels of [3H]vindesine in rats. Cancer Res 37(9):3053–3056
69. Rahmani R, Zhou XJ, Placidi M, Martin M, Cano JP (1990) In vivo and in vitro pharmacokinetics and

metabolism of vincaalkaloids in rat. I. Vindesine (4-deacetyl-vinblastine 3-carboxyamide). Eur J Drug Metab Pharmacokinet 15(1):49–55
70. Zhou XJ, Martin M, Placidi M, Cano JP, Rahmani R. (1990) In vivo and in vitro pharmacokinetics and metabolism of vincaalkaloids in rat. II. Vinblastine and vincristine. Eur J Drug Metab Pharmacokinet 15(4):323–332
71. Leveque D, Quoix E, Dumont P, Massard G, Hentz JG, Charloux A et al (1993) Pulmonary distribution of vinorelbine in patients with non-small-cell lung cancer. Cancer Chemother Pharmacol 33(2):176–178
72. Owellen RJ, Root MA, Hains FO (1977) Pharmacokinetics of vindesine and vincristine in humans. Cancer Res 37(8 Pt 1):2603–2607
73. van Asperen J, Schinkel AH, Beijnen JH, Nooijen WJ, Borst P, van Tellingen O. (1996) Altered pharmacokinetics of vinblastine in Mdr1a P-glycoprotein-deficient Mice. J Natl Cancer Inst 88(14):994–999
74. Zhou XJ, Placidi M, Rahmani R (1994) Uptake and metabolism of vinca alkaloids by freshly isolated human hepatocytes in suspension. Anticancer Res 14(3A):1017–1022
75. Zhou-Pan XR, Seree E, Zhou XJ, Placidi M, Maurel P, Barra Y et al (1993) Involvement of human liver cytochrome P450 3A in vinblastine metabolism: drug interactions. Cancer Res 53(21):5121–5126
76. Gidding CE, Kellie SJ, Kamps WA, de Graaf SS (1999) Vincristine revisited. Crit Rev Oncol Hematol 29(3):267–287
77. Villikka K, Kivisto KT, Maenpaa H, Joensuu H, Neuvonen PJ (1999) Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumors. Clin Pharmacol Ther 66(6):589–593
78. Yao D, Ding S, Burchell B, Wolf CR, Friedberg T (2000) Detoxication of vinca alkaloids by human P450 CYP3A4-mediated metabolism: implications for the development of drug resistance. J Pharmacol Exp Ther 294(1): 387–395
79. Gillies J, Hung KA, Fitzsimons E, Soutar R (1998) Severe vincristine toxicity in combination with itraconazole. Clin Lab Haematol 20(2):123–124
80. Owellen RJ, Hartke CA, Hains FO (1977) Pharmacokinetics and metabolism of vinblastine in humans. Cancer Res 37(8 Pt 1):2597–2602
81. Jehl F, Quoix E, Leveque D, Pauli G, Breillout F, Krikorian A et al (1991) Pharmacokinetic and preliminary metabolic fate of navelbine in humans as determined by high performance liquid chromatography. Cancer Res 51(8):2073–2076
82. Budman DR (1997) Vinorelbine (Navelbine): a third-generation vinca alkaloid. Cancer Invest 15(5): 475–490
83. Bender RA, Castle MC, Margileth DA, Oliverio VT (1977) The pharmacokinetics of [3H]-vincristine in man. Clin Pharmacol Ther 22(4):430–435
84. Krikorian A, Rahmani R, Bromet M, Bore P, Cano JP (1989) Pharmacokinetics and metabolism of Navelbine. Semin Oncol 16(2 Suppl 4):21–25
85. Van den Berg HW, Desai ZR, Wilson R, Kennedy G, Bridges JM, Shanks RG (1982) The pharmacokinetics of vincristine in man: reduced drug clearance associated with raised serum alkaline phosphatase and dose-limited elimination. Cancer Chemother Pharmacol 8(2): 215–219
86. Bollini P, Riva R, Albani F, Ida N, Cacciari L, Bollini C et al (1983) Decreased phenytoin level during antineoplastic therapy: a case report. Epilepsia 24(1):75–78
87. Chabner B, Longo DL (2006) Cancer chemotherapy and biotherapy: principles and practice, 4th edn. Lippincott Williams and Wilkins, Philadelphia
88. Jackson DV Jr, McMahan RA, Pope EK, Case LD, Cooper MR, Kaplon MK et al (1986) Clinical trial of folinic acid to reduce vincristine neurotoxicity. Cancer Chemother Pharmacol 17(3):281–284
89. Jackson DV Jr, Richards F 2nd, Spurr CL, Long TR, Rardin DA, Albertson DA et al (1984) Hepatic intra-arterial infusion of vincristine. Cancer Chemother Pharmacol 13(2):120–122
90. Robieux I, Sorio R, Borsatti E, Cannizzaro R, Vitali V, Aita P et al (1996) Pharmacokinetics of vinorelbine in patients with liver metastases. Clin Pharmacol Ther 59(1):32–40
91. Bradley WG, Lassman LP, Pearce GW, Walton JN (1970) The neuromyopathy of vincristine in man. Clinical, electrophysiological and pathological studies. J Neurol Sci 10(2):107–131
92. Tatsuta T, Naito M, Oh-hara T, Sugawara I, Tsuruo T (1992) Functional involvement of P-glycoprotein in blood-brain barrier. J Biol Chem 267(28):20383–20391
93. Kaplan RS, Wiernik PH (1982) Neurotoxicity of antineoplastic drugs. Semin Oncol 9(1):103–130
94. Quasthoff S, Hartung HP (2002) Chemotherapy-induced peripheral neuropathy. J Neurol 249(1):9–17
95. Legha SS (1986) Vincristine neurotoxicity. Pathophysiology and management. Med Toxicol 1(6):421–427
96. Sharma RK (1988) Vincristine and gastrointestinal transit. Gastroenterology 95(5):1435–1436
97. Gottlieb RJ, Cuttner J (1971) Vincristine-induced bladder atony. Cancer 28(3):674–675
98. Hirvonen HE, Salmi TT, Heinonen E, Antila KJ, Valimaki IA (1989) Vincristine treatment of acute lymphoblastic leukemia induces transient autonomic cardioneuropathy. Cancer 64(4):801–805
99. Subar M, Muggia FM (1986) Apparent myocardial ischemia associated with vinblastine administration. Cancer Treat Rep 70(5):690–691
100. Desai ZR, Van den Berg HW, Bridges JM, Shanks RG (1982) Can severe vincristine neurotoxicity be prevented? Cancer Chemother Pharmacol 8(2):211–214
101. Boyle FM, Wheeler HR, Shenfield GM (1996) Glutamate ameliorates experimental vincristine neuropathy. J Pharmacol Exp Ther 279(1):410–415
102. Hellmann K, Hutchinson GE, Henry K (1987) Reduction of vincristine toxicity by Cronassial. Cancer Chemother Pharmacol 20(1):21–25
103. Slyter H, Liwnicz B, Herrick MK, Mason R (1980) Fatal myeloencephalopathy caused by intrathecal vincristine. Neurology 30(8):867–871
104. Bellone JD (1981) Treatment of vincristine extravasation. JAMA 245(4):343

105. Fedeli L, Colozza M, Boschetti E, Sabalich I, Aristei C, Guerciolini R et al (1989) Pharmacokinetics of vincristine in cancer patients treated with nifedipine. Cancer 64(9):1805–1811
106. Ballen KK, Weiss ST (1988) Fatal acute respiratory failure following vinblastine and mitomycin administration for breast cancer. Am J Med Sci 295(6):558–560
107. Hohneker JA (1994) A summary of vinorelbine (Navelbine) safety data from North American clinical trials. Semin Oncol 21(5 Suppl 10):42–46; discussion 46–47
108. Samuels BL, Mick R, Vogelzang NJ, Williams SF, Schilsky RL, Safa AR et al (1993) Modulation of vinblastine resistance with cyclosporine: a phase I study. Clin Pharmacol Ther 54(4):421–429
109. Tobe SW, Siu LL, Jamal SA, Skorecki KL, Murphy GF, Warner E. (1995) Vinblastine and erythromycin: an unrecognized serious drug interaction. Cancer Chemother Pharmacol 35(3):188–190
110. Thant M, Hawley RJ, Smith MT, Cohen MH, Minna JD, Bunn PA et al (1982) Possible enhancement of vincristine neuropathy by VP-16. Cancer 49(5):859–864
111. Sathiapalan RK, El-Solh H (2001) Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. Pediatr Hematol Oncol 18(8):543–546
112. Crom WR, de Graaf SS, Synold T, Uges DR, Bloemhof H, Rivera G et al (1994) Pharmacokinetics of vincristine in children and adolescents with acute lymphocytic leukemia. J Pediatr 125(4):642–649
113. Chan JD (1998) Pharmacokinetic drug interactions of vinca alkaloids: summary of case reports. Pharmacotherapy 18(6):1304–1307
114. Jarosinski PF, Moscow JA, Alexander MS, Lesko LJ, Balis FM, Poplack DG (1988) Altered phenytoin clearance during intensive chemotherapy for acute lymphoblastic leukemia. J Pediatr 112(6): 996–999