THE CLINICAL PHARMACOLOGY AND USE OF ANTIMICROTUBULE AGENTS IN CANCER CHEMOTHERAPEUTICS

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Abstract—Although there has been a rapid expansion of the number of classes of compounds with antineoplastic activity, few have played a more vital role in the curative and palliative treatment of cancers than the antimicrotubule agents. Although the vinca alkaloids have been the only subclass of antimicrotubule agents that have had broad experimental and clinical applications in oncologic therapeutics over the last several decades, the taxanes, led by the prototypic agent taxol, are emerging as another very active class of antimicrotubule agents. After briefly reviewing the mechanisms of antineoplastic action and resistance, this article comprehensively reviews the clinical pharmacology, therapeutic applications, and clinical toxicities of selected antimicrotubule agents.

CONTENTS

Abbreviations: ALL = acute lymphocytic leukemia; ANLL = acute nonlymphocytic leukemia; AUC = area under the time-versus-concentration curve; DNA = deoxyribose nucleic acid; GM-CFC = granulocyte-macrophage colony-forming cell; GTP = guanosine triphosphate; HSR = hypersensitivity reaction; MAPs = microtubule-associate proteins; NCI = National Cancer Institute; NVB = vinorelbine (Navelbine); SIADH = syndrome of inappropriate secretion of antidiuretic hormone; $t_{\frac{1}{2}}$ = half-life; VBL = vinblastine; VCR = vincristine; VDS = vindesine.

1. INTRODUCTION

Microtubules are among the most strategic subcellular targets of anticancer chemotherapeutics. Like DNA, microtubules are ubiquitous to all cells. Although they are primarily recognized as being important in mitotic functions, microtubules also play critical roles in many interphase and maintenance functions in cells such as maintenance of cell shape and scaffolding, intracellular transport, secretion, and possible relay of signals between cell surface receptors and the nucleus (Edelman, 1976; Dustin, 1980; Crossin and Carney, 1981; Otto et al., 1981). Interestingly, antimicrotubule agents are all structurally complex natural products or semisynthetic compounds. They are among the most important of anticancer drugs and have significantly contributed to the therapy of most curable neoplasms such as Hodgkin's and non-Hodgkin's lymphomas, germ cell tumors and childhood leukemia (Loehrer et al., 1988b; DeVita et al., 1989; Hellman et al., 1989; Henderson et al., 1990). They are also extremely useful in the palliative treatment of many other cancers. Despite their promise, only a few antimicrotubule agents have been developed over the last decade and only two vinca alkaloids, vincristine and vinblastine, are officially approved for use and are widely available for oncologic therapy in North America and Europe. However, there has recently been a resurgence of interest in these compounds. This has led to the identification and development of several novel vinca alkaloids like vinorelbine (Navelbine), as well as new classes of antimicrotubule agents such as taxanes, dolostatins, and rhizoxin which possess novel mechanisms of cytotoxic action, unique antitumor spectra in vitro and/or in the clinic, and potentially improved therapeutic indices. This review will focus on those vinca alkaloids and taxanes in which ample clinical and preclinical experience exists.

2. VINCA ALKALOIDS

2.1. GENERAL

The vinca alkaloids are natural or semisynthetic compounds which are present in minute quantities in the plant Catharanthus roseus G. Don (formerly Vinca rosea Linn.), commonly called the periwinkle. The compounds were originally screened by pharmaceutical chemists because of their use as hypoglycemic agents in several parts of the world. However, their hypoglycemic activity turned out to be of miniscule importance compared to their cytotoxic properties.

Since the 1960s, only two vinca alkaloids, vincristine (VCR) and vinblastine (VBL), have been officially approved for the treatment of malignant disorders in the United States. Both VCR and VBL are large, dimeric compounds with similar but complex structures (Fig. 1). They are composed of an indole nucleus (the catharanthine portion) and a dihydroindole nucleus (the vindoline portion). VCR and VBL are structurally identical with the exception of the substitutent attached to the nitrogen of the vindoline nucleus where VCR possesses a formyl group and VBL has a methyl group. However, VCR and VBL differ dramatically in their antitumor spectrum and clinical toxicities.

A third vinca alkaloid analog, vindesine (VDS; desacetyl vinblastine carboxyamide), a synthetic derivative and human metabolite of VBL, was introduced into clinical trials in the 1970s. Although VDS has demonstrated activity against several malignancies, most notably non-small cell lung cancer, it has only been available for investigational purposes and its future is uncertain. Other vinca alkaloids with antitumor activity include vinleurosine and vinrosidine; however, further clinical development of these
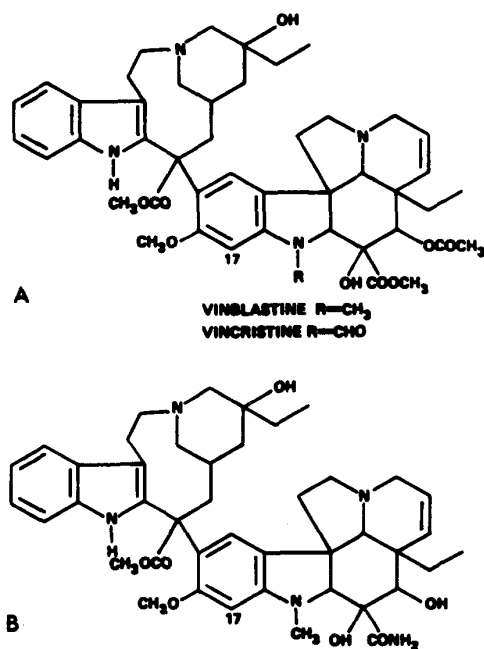

FIG. 1. Structures of vincristine and vinblastine (A); vindesine (B).

agents has been abandoned due to their exceptional toxicities (Creasey, 1975). Recently, semi-synthetic derivatives of VBL, specifically vinorelbine (Navelbine; NVB) and vinzolidine, have also entered clinical development and appear to be exciting for several reasons. These compounds, especially NVB, have demonstrated activity in neoplasms that are refractory to conventional agents. In addition, both NVB and vinzolidine are oral preparations in contrast to all other available vinca alkaloids which can only be administered by parenteral routes.

The clinical pharmacology, toxicology, and clinical applications of the vinca alkaloids, VCR, VBL, VDS, and NVB, will be discussed in this section. Relevant aspects of vinzolidine's clinical pharmacology and early phase I/II trials have been published (Budman et al., 1984; Kreis et al., 1986; Taylor et al., 1990; Budman et al., 1991). Extensive reviews of the identification, isolation, and characterization of the vinca alkaloids are also available (Johnson et al., 1963; Neuss et al., 1964; Creasy et al., 1975).

2.2. MECHANISMS OF ACTION

The vinca alkaloids induce cytotoxicity by direct interactions with tubulin which is the basic protein subunit of microtubules (Johnson et al., 1963; Olmstead and Borisy, 1973; Luduena et al., 1977; Dustin, 1980). Other biochemical effects that have been reported for the vinca alkaloids include: (a) competition for transport of amino acids into cells; (b) inhibition of purine biosynthesis; (c) inhibition of RNA, DNA, and protein synthesis; (d) disruption of lipid metabolism; (e) inhibition of glycolysis; (f) alterations in the release of antidiuretic hormone; (g) inhibition of release of histamine by mast cells and enhanced release of epinephrine; and (h) disruption in the integrity of the cell membrane and membrane functions. Comprehensive reviews on these various effects have been published (Creasy, 1975, Beck, 1984).

Microtubules are ubiquitous in eukaryotic cells and vital to the performance of many critical functions including maintenance of cell shape, mitosis, meiosis, secretion, intracellular transport, and axonal transport. Many of the unique pharmacologic interactions of drugs with microtubules are due to a dynamic equilibrium between microtubules and tubulin dimers (Bryan, 1974; Dustin, 1980). Critical messages in the cell, including those related to cell cycle traverse, influence net microtubule polymerization. Vinca alkaloids exert their antimicrotubule effects by binding to a site on tubulin that is distinctly different from the binding sites of colchicine, podophyllotoxin, and taxol (Bryan, 1972a; Owellen et al., 1972; Wilson et al., 1975; Bhattacharyya and Wolff, 1976; Huang et al., 1985). The vinca alkaloids bind to specific sites on tubulin with a binding constant of 5.6×10^{-5} M (Na and Timasheff, 1986) and initiate a sequence of events that lead to disruption of microtubules.

The binding of the vinca alkaloids to tubulin, in turn, prevents the polymerization of these subunits into microtubules. The subunits then form highly ordered paracrystalline arrays of tubulin that are often termed 'paracrystals' (Bryan, 1972b; Manfredi and Horowitz, 1984a) which contain one mole of bound drug per mole of tubulin (Bensch and Malawista, 1969). The net effects of these processes include the blockage of the polymerization of tubulin into microtubules which may eventually lead to the inhibition of vital cellular processes and cell death.

Although most evidence indicates that mitotic arrest is the principal cytotoxic effect of the vinca alkaloids, there is also evidence suggesting that the lethal effects of these agents may be attributable in part to effects on other phases of the cell cycle. The vinca alkaloids appear to be cytotoxic to non-proliferating cells in vitro and in vivo in both G_1 and S cell cycle phases (Madoc-Jones and Mauro, 1968; Strychmans et al., 1973; Rosner et al., 1975).

2.3. MECHANISMS OF RESISTANCE

Resistance to the vinca alkaloids develops fairly rapidly in vitro in the presence of these agents. To date, two mechanisms of resistance have been described. The first mechanism involves mutations in either the alpha or beta subunits of tubulin, leading to decreased vinca alkaloid binding (Cabral et al., 1986; Brewer and Warr, 1987). The second, more well characterized mechanism of resistance involves the general multi-drug resistance (mdr) phenotype that confers broad resistance to many unrelated classes of large, bulky natural product antineoplastic agents including the antitumor antibiotics, vinca alkaloids, colchicine, and taxol, and the epipodophyllotoxins (Juliano and Ling, 1976; Wilkoff and Dulmadge, 1978; Beck et al., 1979; Riordan and Ling, 1979; Inaba et al., 1984; Conter and Beck, 1984; Gupta, 1985; Beck, 1987; Fojo et al., 1987a,b; Greenberger et al., 1987; Hamada et al., 1987; Choi et al., 1988; Moscow and Cowan, 1988). Cells with mdr phenotype possess an increased capacity to expel natural products by virtue of increased amounts of membrane phosphoglycoproteins (P-glycoproteins) such as the P-170 membrane glycoprotein that functions as a drug efflux pump (Hamada et al., 1987). A substantial number of unrelated compounds, including calcium channel antagonists (Tsuruo, 1983; Brewer and Warr, 1987), phenothiazines and other 'calmodulin antagonists' (Tsuruo et al., 1983; Akiyama et al., 1986), antiarrhythmic agents such as quinidine and amiodarone (Tsuruo et al., 1984; Inaba and Earuyama, 1988), cephalosporins (Gosland et al., 1989), and cyclosporin A (Slater et al., 1986) have been demonstrated to reverse drug resistance related to the mdr phenotype. Interestingly, the ability of the calcium channel blocker verapamil or cyclosporin A to reverse mdr resistance does not appear to be

related to either calcium channel antagonism or immunomodulation since inactive isomers are considerably more active in reversing this type of resistance (Gruber et al., 1988; Twentyman, 1988).

2.4. VINCRISTINE

2.4.1. Clinical Pharmacology

Relative to their broad clinical use, there are limited data available about the pharmacology of the vinca alkaloids in humans compared to other classes of antineoplastic agents. This has primarily been due to a lack of sensitive assays capable of measuring minute plasma concentrations which result from the wide distribution of mg doses of these agents. Early animal and human studies used radiolabeled vinca alkaloids, with further separation of parent drug and metabolites by high-pressure liquid chromatography (HPLC) (Castle et al., 1976; Bender et al., 1977; Culp et al., 1977; El Dareer et al., 1977; Owellen et al., 1977a,b; Jackson et al., 1978; Owellen and Hartke, 1985). More recently, studies using sensitive radioimmunoassays (RIA) and enzyme-linked immunosorbent assay (ELISA) methods, which may be able to detect picomolar concentrations, have been able to overcome these problems (Nelson et al., 1979, 1980; Hande et al., 1980; Jackson et al., 1980, 1981a; Sethi et al., 1981b; Sethi and Kimball, 1981; Nelson, 1982; Hacker et al., 1984; Rahmani et al., 1985; Labinjoki et al., 1986; Ratain and Vogelzang, 1986, 1987).

Following standard doses of VCR administered as a bolus intravenous injection, peak plasma VCR levels approach $0.4 \mu M$ (Bender et al., 1977). VCR's plasma distribution is characterized by triexponential kinetics with a distribution (alpha) half-life ($t_{\frac{1}{2}}$) of less than 5 min owing to extensive and rapid tissue binding. Beta phase $t_{\frac{1}{2}}$ values have been reported to range from 50 to 155 min and terminal $t_{\frac{1}{2}}$ values have varied even more profoundly, from 23 ± 17 to 85 ± 65 hr (Owellen et al., 1977b; Nelson et al., 1980; Jackson et al., 1981b; Sethi et al., 1981b; Nelson, 1982). Similar pharmacokinetic parameters have been noted in children (Sethi and Kimball, 1982). When the pharmacologic behavior of VCR has been studied using ^{3}H-VCR coupled with purification by HPLC, alpha, beta, and terminal $t_{\frac{1}{2}}$ have been determined to be 0.85, 7.4, and 64 min, respectively (Bender et al., 1977). In one comparative pharmacokinetic study of VCR, VBL, and VDS, VCR had the longest terminal $t_{\frac{1}{2}}$, 85.0 ± 68.9 hr, versus 24.8 ± 7.5 hr for VBL and 24.2 ± 10.4 hr for VDS (Nelson et al., 1980; Nelson, 1982). The apparent volumes of distribution (V_d) have also been high ($V_d$central of 0.328 ± 0.106 l/kg and $V_d$gamma, 8.42 ± 3.17 l/kg for VCR), indicating extensive tissue binding (Nelson et al., 1980; Nelson, 1982). In addition, marked differences in serum clearance rates have been noted with VCR having the slowest clearance (0.106 ± 0.061 l/kg-hr), VBL the

highest (0.740 ± 0.317 l/kg-hr), and VDS an intermediate value (0.252 ± 0.100 l/kg-hr) (Nelson et al., 1980; Nelson, 1982). It has been postulated that VCR's longer terminal half-life and lower plasma clearance rate compared to other vinca alkaloids might account for its greater neurotoxic effects (Nelson et al., 1980; Nelson 1982).

There has been a considerable interest in the administration of VCR on protracted continuous infusion schedules based on the likelihood that these schedules more closely simulate optimal in vitro conditions required for cytotoxicity compared to bolus schedules (Jackson, 1990). The cytotoxicity of the vinca alkaloids appears to be dependent not only on drug concentration, but on duration of treatment (Jackson and Bender, 1979; Hill and Whelan, 1980; Ferguson et al., 1984; Ludwig et al., 1984; Jackson, 1990). VCR concentrations in the range of 100 nM are only briefly achieved after intravenous bolus injections and levels typically decline to less than 10 nM by 2 to 4 hr approaching 1 nM by 48 to 72 hr (Nelson et al., 1980; Jackson et al., 1981b). When compared to conditions required for cytotoxicity in vitro, though, treatment with 100 nM VCR for 3 hr is required to kill 50% of L1210 murine or CEM human lymphoblastic leukemias, whereas 6 to 12 hr of treatment is required to achieve this degree of cytotoxicity at 10 nM and no lethal effects occurs with VCR concentrations below 2 nM (Jackson and Bender, 1979). Interestingly, a 0.5 mg intravenous bolus injection of VCR followed by a continuous infusion at doses of 0.5 to 1.0 mg/m²/day for 5 consecutive days has typically produced steady-state VCR concentrations ranging from 1 nM to 10 nM and half-lives after discontinuation of the infusions have ranged from 10.5 hr (1.0 mg/m²) to 21.7 hr (0.5 mg/m²) (Jackson et al., 1981b). Although peak VCR plasma concentrations achieved with continuous infusions have generally been lower than levels achieved with bolus injections, continuous infusions have produced greater total drug exposure above a critical threshold concentration (Jackson et al., 1981b).

The tissue distribution of VCR has been investigated in several animal species. In the dog and the rat, the spleen appears to concentrate VCR to a greater extent than any other tissue (Owellen and Donigian, 1972; Castle et al., 1976). In the monkey, the tissue with the highest VCR concentration has been the pancreas (El Dareer et al., 1977). Although VCR has been demonstrated to rapidly enter the central nervous system of primates after intravenous injection, with VCR levels above 1 nM maintained in cerebrospinal fluid for longer than 72 hr in one study (El Dareer et al., 1977), most investigations using rats, dogs, monkeys, and humans have indicated that VCR penetrates poorly through the blood–brain barrier (Castle et al., 1976; El Dareer et al., 1977; Jackson et al., 1980, 1981a). In humans, cerebrospinal fluid levels have been 20- to 30-fold lower than concurrent plasma concentrations and have never exceeded

1.1 nM (Jackson et al., 1981a). Approximately 48% of VCR is bound to serum proteins (Bender et al., 1977). VCR also undergoes extensive binding to formed blood elements, especially platelets and red blood cells, which has led to the use of VCR-loaded platelets for treating disorders of platelet consumption such as idiopathic thrombocytopenia purpura (see Section 2.4.3, Clinical Applications).

VCR is primarily metabolized in the liver and excreted in the feces (Bender et al., 1977; Jackson et al., 1978). Within 72 hr after the administration of radiolabeled VCR, 12% of the total labeled material is excreted in the urine, 50% of which consists of metabolites; and approximately 70% is excreted in the feces, 40% of which consists of metabolites (Bender et al., 1977). VCR rapidly concentrates in the bile with an initial bile : plasma concentration ratio of 100 : 1 which declines to 20 : 1 at 72 hr post-injection (Jackson et al., 1978). Metabolic products accumulate rapidly in the bile such that only 46.5% of the total biliary product is the unmetabolized parent compound (Jackson et al., 1978). Many studies in both man (Bender et al., 1977, Jackson et al., 1978, Sethi et al., 1981a,b) and animals (Castle et al., 1976, Houghton et al., 1984) have demonstrated that approximately 6 to 11 metabolites are produced. The structures of all these metabolites have not been definitely identified; however, analytical studies of the products formed by incubating VCR with dog bile have identified 4-deacetylVCR as a principal metabolite (Sethi and Thimmaiah, 1985; Thimmaiah and Sethi, 1990). In addition, 4-deacetylvincristine (Houghton et al., 1984) and N-deformylVCR (Sethi et al., 1981a) have been isolated from human bile. 4'-Deoxy-3'-hydroxyVCR and 3',4'-epoxyvincristine N-oxide have also been tentatively identified from in vitro incubation of VCR with bile from dogs (Thimmaiah and Sethi, 1990).

2.4.2. Dose and Schedule

VCR is routinely administered to children as a bolus intravenous injection at doses of 2.0 mg/m² weekly (Livingston and Carter, 1970). For adults, the conventional weekly dose is 1.4 mg/m². A restriction of the absolute single dose of VCR to 2.0 mg/m² has been adopted by many clinicians over the last several decades, presumptively based on reports of exceptional neurotoxicity at higher doses. Nevertheless, the origin of this restriction has recently been investigated and felt to be largely based on empiricism (Sulkes and Collins, 1987). Available evidence suggests that this absolute restriction should be reconsidered (Sulkes and Collins, 1987). It has readily been appreciated that cumulative dose may be a more critical variable than single dose; however, wide interpatient variability exists and some patients are able to tolerate much higher VCR doses with little or no toxicity (Costa et al., 1962, Holland et al., 1973). This may be due to significant interindividual differ-

ences in areas under the time-versus-concentration curves (AUC) which have been found to vary by as much as 11-fold (Desai et al., 1982; Van den Berg et al., 1982). However, this explanation does not justify capping VCR doses at 2.0 mg.

It is commonly believed that subsequent doses of VCR should be adjusted based on toxicity; however, doses should not be reduced for a mild peripheral neuropathy, particularly if VCR is being used in a regimen with curative intent. Instead, VCR may have to be held for signs and symptoms indicative of more serious neurotoxicity, including severe symptomatic sensory changes, motor and/or cranial nerve deficits, and ileus, until these toxicities resolve. In clearly palliative settings, more liberal attitudes about dose reduction or lengthening dosing intervals may be justified for moderate neurotoxicity.

Based on in vitro data indicating that the duration of VCR treatment above a critical threshold concentration is an important determinant for cytotoxicity (Jackson and Bender, 1979), phase I/II trials in adults have evaluated prolonged continuous infusion schedules (Jackson, 1990). Following a 0.5 mg/m² intravenous injection of VCR, total daily VCR doses of 0.25 to 0.50 mg/m² as a continuous infusion for 5 consecutive days have generally been well tolerated (Weber et al., 1979; Hopkins et al., 1983; Jackson et al., 1984b, 1985a,b, 1986a; Pinkerton et al., 1985; Yau et al., 1985; Jackson, 1990). In pediatric patients, the continuous infusion of VCR for 5 consecutive days has permitted a twofold increase in the dose that could be safely administered without major toxicity compared to bolus administration schedules (Pinkerton et al., 1988).

VCR is a potent vesicant and should not be administered intramuscularly, subcutaneously, or intraperitoneally. VCR has been accidentally administered into the cerebrospinal fluid resulting in rapid death (Slyter et al., 1980; Gaidys et al., 1983; Williams et al., 1983; Dyke, 1989). VCR (0.4 mg/day for 5 consecutive days) has also been administered by the hepatic intra-arterial route to 6 patients with metastatic liver disease (colon cancer (5); non-Hodgkin's lymphoma (1)) (Jackson et al., 1984c). No objective responses were observed, and toxicities, including substantial neurotoxicity (confusion, weakness, ileus, aphasia, postural hypotension, urinary incontinence), were very severe in some patients. Diarrhea, a rare toxicity of VCR on bolus schedules, was also observed in one third of the patients.

Although it has not been carefully evaluated, an apparently major role of the liver in the disposition and metabolism of VCR (see Section 2.4.1., Clinical Pharmacology) indicates that dose modifications should be considered for patients with hepatic dysfunction (Van den Berg et al., 1982). To date, firm guidelines for dose modifications have not been established; however, a 50% dose reduction is often recommended for patients with plasma in bilirubin concentrations above 3 mg/dl.

2.4.3. *Clinical Applications*

2.4.3.1. *Leukemia.* The recognition of VCR's significant activity in acute lymphocytic leukemia (ALL) in the 1960s was one of the events that opened the door to the modern era of cancer chemotherapy. The combination of VCR and prednisone continues to be the cornerstone of remission induction treatment for ALL in children and adults. VCR can be given in optimal therapeutic doses to patients with ALL with only mild inhibition of granulopoiesis and thrombopoiesis. Although many trials of VCR administered on various schedules and doses for remission induction have been conducted, a single intravenous bolus dose of 2 mg/m^2 weekly has become the consensus schedule of administration, with the qualification expressed by many that the total weekly dose not exceed 2 mg (see Section 2.4.2., Dose and Schedule). More frequent bolus injection (Carbone *et al.*, 1963) and continuous infusion schedules have greater antitumor activity in this disease (Greenberg and Holland, 1976), but the increased toxicity of these regimens has exceeded any increases in antitumor activity. The combination of VCR and prednisone as initial therapy is capable of including complete remissions in over 85% of pediatric patients with ALL (Mauer and Simone, 1976; Aur *et al.*, 1978) and between 36% and 67% in adults (Amadori *et al.*, 1980; Willemze *et al.*, 1980; Hess and Zirkle, 1982). However, the combination of VCR and prednisone is rarely used alone as initial induction therapy since the rate and duration of these responses have been demonstrated to be increased by the addition of other agents such as L-asparaginase and the anthracyclines (Hagbin *et al.*, 1974; Ortega *et al.*, 1977; Sachman-Muriel *et al.*, 1978; Willemze *et al.*, 1980; Gottlieb *et al.*, 1984). On the other hand, VCR with or without corticosteroids, has yet to establish itself in remission maintenance therapy (Colebach *et al.*, 1968), but may add to the maintenance afforded by antimetabolites when given intermittently (Chevalier and Glidewell, 1967; Jones *et al.*, 1977; Leiken *et al.*, 1968).

Similar VCR-prednisone-based regimens have also been used to treat acute lymphoblastic crisis of chronic myelogenous leukemia (Rosenthal *et al.*, 1977) and Philadelphia chromosome positive childhood ALL (Crist *et al.*, 1990). VCR is not as active in the treatment of acute nonlymphocytic leukemia (ANLL), especially in adults. In early studies in ANLL, single agent therapy with VCR was associated with a 21% complete response rate and a 51% overall response rate, but the majority of the responses occurred in children (Livingston and Carter, 1970).Although VCR has been incorporated into several induction and post-remission therapies for adult ANLL (Glucksberg *et al.*, 1981; Yates *et al.*, 1982; Weinstein *et al.*, 1983; Sauter *et al.*, 1984; Priesler *et al.*, 1987), the drug is not generally used in most conventional treatment regimens. VCR is more commonly employed, albeit infrequently, in childhood ANLL in combination with other agents, principally cytosine arabinoside, an anthracycline (usually daunorubicin), 6-thioguanine, and 5-azacytidine.

2.4.3.2. *Hodgkin's lymphoma.* VCR has also had a substantial impact on the curative treatment of both Hodgkin's and non-Hodgkin's lymphomas in adults and children. In early studies of VCR used as a single agent in all forms of lymphoma, responses were observed in 50% to 60% of patients (Livingston and Carter, 1970). As with the leukemias, however, the incidences of complete and durable responses have been substantially lower with single agent therapy (Costa *et al.*, 1962; Bohannon *et al.*, 1963; Carbone *et al.*, 1963; Gailani, 1963; Shaw *et al.*, 1964; Selawry *et al.*, 1968; Livingston and Carter, 1970). In 1967, however, a report on the use of VCR (Oncovin) in combination with nitrogen mustard, procarbazine, and prednisone (MOPP) demonstrated that combination chemotherapy could produce a high rate (80%) of complete remissions in advanced Hodgkin's disease (a four-fold increase over the best results achieved with single agents), and remissions were durable (DeVita and Serpick, 1967; DeVita *et al.*, 1970; Lowenbraun *et al.*, 1970; DeVita, 1981). Each agent in MOPP was selected based on single agent antitumor activity and to minimize potential overlapping toxicities. Although VBL may have been the favored vinca alkaloid in lymphomas at that time, VCR was selected because it was associated with less myelosuppression. A 20 year follow-up report of the original series of patients treated with MOPP revealed that the original study population was even slanted towards poorer prognostic variables (Longo *et al.*, 1986). Of those patients who achieved a complete remission, 64% and 54% have remained alive and continuously disease free, respectively, after 20 years. In the original MOPP regimen, VCR was administered as a 1.4 mg/m^2 intravenous bolus weekly for two consecutive weeks every 28 days without dose capping at 2.0 mgs. A sliding scale based on neurotoxic symptoms was used to adjust VCR dose. Despite considerable acute peripheral neurotoxicity observed in the original study, toxicity slowly resolved in most patients after therapy was discontinued and no patients were permanently paralyzed.

In the decade following the success of MOPP, many other regimens were designed to reduce the side-effects of MOPP by substituting or adding additional drugs and to improve on MOPP's antitumor activity by either increasing dose intensity and/or alternating MOPP with other non-cross resistant regimens. Almost all of these modified regimens included a vinca alkaloid, either VCR or VBL. Of those modified regimens containing VCR, none have consistently demonstrated superiority to MOPP. Modified MOPP alternatives containing VCR that

have been evaluated in Hodgkin's disease include COPP (cyclophosphamide, VCR, procarbazine and prednisone) (Cooper et al., 1984; Propert et al., 1986); LOPP (chlorambucil, VCR, procarbazine and prednisone) (Hancock, 1986); and B–MOPP (bleomycin added to MOPP) (Coltman et al., 1985). Non-cross resistant alternative regimens have included MOPP–ABVD (MOPP alternating with ABVD (Adriamycin, bleomycin, VBL and dacarbazine) (Santoro et al., 1982a; Bonadonna et al., 1986; Canellos et al., 1988); MOP–BAP (nitrogen mustard, VCR, bleomycin, adriamycin, prednisone) (Jones et al., 1983); and MOPP–ABV, a MOPP–ABVD variant in which dacarbazine is omitted and all the agents are given in the first 8 days rather than alternating on a monthly basis (Klimo and Connors, 1985a).

2.4.3.3. *Non-Hodgkin's lymphoma.* VCR has also been an important drug in multi-agent chemotherapy regimens used in the palliative treatment of indolent lymphomas and in both the palliative and curative treatment of aggressive lymphomas. CVP (cyclophosphamide, VCR, prednisone) was among the first popular combination regimen used to treat both indolent and aggressive lymphomas. Similar to most combination regimens in advanced indolent lymphomas, complete responses were achieved with CVP in approximately 70% of patients. However, patients relapsed continuously over time and fewer than 10% did not develop progressive disease over 5 years (Schein et al., 1975). Although more aggressive regimens such as M–BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, VCR and dexamethasone) (Anderson et al., 1984), the M-2 regimen (BCNU, VCR, melphalan and prednisone) (Case, 1984), COPP (cyclophosphamide, VCR, prednisone and procarbazine) (Ezdinli et al., 1985), and ProMACE/MOPP (etoposide, adriamycin, cyclophosphamide and methotrexate alternating with MOPP) (Young et al., 1987) have achieved a higher complete response rate with increased durability in advanced indolent lymphomas, the mean survival of untreated and/or palliated patients has been quite long and the improvements in complete response rates and response duration have not yet translated into significant survival advantages. Although novel agents such as fludarabine have recently been found to be quite active in the chronic lymphocytic leukemia (CLL), VCR-based regimens such as CVP are still commonly used in both first-line and salvage therapies (Lipman and Votaw, 1978).

In contrast to the situation in the advanced indolent lymphomas, VCR-containing combination regimens have made a substantial impact on the curative therapy of intermediate and aggressive non-Hodgkin's lymphomas. Although regimens such as CVP have been somewhat effective in treating aggressive lymphomas, the proportion of patients who achieve durable complete remissions has been low. Initial attempts to improve on these results focused

on adding active agents to a cyclophosphamide-VCR-prednisone backbone and were modestly successful. These efforts resulted in regimens like C–MOPP (cyclophosphamide, VCR, prednisone, procarbazine) (DeVita et al., 1975) and COMLA (cyclophosphamide, VCR, methotrexate, leucovorin and cytosine arabinoside) (Berd et al., 1975) which induced complete responses in 45% to 50% of patients and a high proportion of these responses were durable.

The addition of anthracyclines to this multi-agent backbone in the early 1970s was the next development in the treatment of the aggressive lymphomas. These efforts resulted in higher overall response and complete response rates as well as higher percentages of durable responses. Practically all of these combinations contained VCR such as CHOP (cyclophosphamide, doxorubicin, VCR, prednisone) (Armitage et al., 1984) and BACOP (bleomycin, doxorubicin, cyclophosphamide, VCR, prednisone) (Schein et al., 1976), which were capable of inducing complete responses in approximately 50% of patients, with cures being rendered in one-third of all patients. In the early 1980s, developments focused on multi-agent regimens with increased numbers of agents, increased dose intensity, and methotrexate for central nervous system penetration. These combinations, including m–BACOD and M–BACOD (high or moderate doses of methotrexate, with bleomycin, doxorubicin, cyclophosphamide, VCR, and dexamethasone) (Skarin et al., 1983; Dana et al., 1990), COP–BLAM, COP–BLAM III and CAP–BOP (cyclophosphamide, doxorubicine, VCR, procarbazine, prednisone and bleomycin) (Laurence et al., 1982; Boyd et al., 1988), and ProMACE/MOPP flexitherapy (cyclophosphamide, doxorubicin, etoposide, methotrexate, nitrogen mustard, VCR, prednisone and procarbazine) (Fisher et al., 1983), were capable of achieving complete responses in approximately 75% of all patients and approximately 50% were rendered permanently disease free. In the 1980s, VCR remained an integral component of even more novel multi-agent regimens such as MACOP–B (methotrexate, doxorubicin, cyclophosphamide, VCR and bleomycin) in which intensive therapy is delivered for 12 weeks (Klimo and Connors, 1985b, 1987) and ProMACE–CytaBOM (cyclophosphamide, doxorubicin, etoposide, cytosine arabinoside, bleomycin, VCR, methotrexate and prednisone) (Longo et al., 1991) which has the highest relative dose intensity. Preliminary results have indicated that these programs achieve complete remissions in approximately 80% of patients, with only 20% of complete responders relapsing within the first two years.

VCR has generally been administered as an intravenous bolus injection in most combination regimens for non-Hodgkin's lymphoma and there has been a surprisingly small number of studies evaluating VCR on continuous infusion schedules. Recently, Jackson reviewed the data from five clinical trials in patients

with non-Hodgkin's lymphoma in which single agent infusional therapy with VCR (0.25 to 0.50 mg/m²/day for 5 consecutive days) was associated with a 41% overall response rate in patients who had received prior chemotherapy including VCR by bolus injection (Jackson et al., 1984b; Jackson, 1990). Combination regimens with VCR administered as an infusion rather than as a bolus in previously untreated patients have also been studied. COP–BLAM III and COP–BLAM IV, the most popular of these regimens, have employed VCR as a 1.0 mg/m²/day continuous infusion for 2 consecutive days. These regimens induced complete remissions in 84 to 88% of untreated patients (Coleman et al., 1988). Warrell et al. (1989) administered VCR as a continuous infusion (0.5 mg/m²/day for 3 consecutive days) along with multiple other agents (doxorubicin, bleomycin, and etoposide) and demonstrated complete remissions in 24 of 26 (92%) untreated patients. Kantarjian et al. (1990) also reported that continuous infusions of both VCR and doxorubicin along with dexamethasone (VAD) had significant activity in high-risk patients with acute lymphoblastic leukemia/lymphoma (Kantarjian et al., 1990). In addition, Jackson et al. (1990a) modified the conventional CHOP regimen to include infusional VCR (0.25 mg/m²/day for 5 consecutive days) and observed complete remissions in 54% of patients and long-term remissions in approximately one-third of all patients. No increased neurotoxicity was observed beyond that expected with bolus injection schedules. With antitumor synergy demonstrated for the combination of VCR and etoposide in an animal model (Jackson et al., 1984a), Jackson and colleagues investigated infusional VCR (0.25 mg/m²/day for 5 consecutive days) in combination with either bolus or infusional etoposide in patients with refractory non-Hodgkin's lymphoma (Jackson et al., 1990b). These investigators reported objective responses in 2 of 14 (21%) patients. In addition, infusional VCR (0.75 / mg/m²/day × 2) combined with high dose etoposide (up to 1 g/m²) produced partial responses in 2 of 6 refractory Hodgkin's and non-Hodgkin's lymphoma patients in a phase I study (Jackson et al., 1989).

2.4.3.4. *Plasma cell dyscrasia*. VCR is active in plasma cell dyscrasias and has been incorporated into several treatment schemes (Salmon, 1975; Jackson et al., 1985a). However, there is no clear indication that the addition of VCR to conventional combinations of alkylating agents and prednisone results in improved survival. In addition, there is considerable controversy regarding the effectiveness of complex multi-agent regimens that may or may not contain VCR compared to simpler regimens such as oral melphalan and prednisone or cyclophosphamide and prednisone. The majority of these more complex regimens, including the M-2 regimen (VCR, melphalan, cyclophosphamide, BCNU and prednisone) (Case et al., 1977), VMCP (VCR, melphalan, cyclo-

phosphamide and prednisone) and VBAP (VCR, BCNU, doxorubicin, and prednisone) (Salmon et al., 1983; Blade et al., 1986, 1990) employ VCR as an intravenous bolus injection. In untreated, refractory or relapsing patients with multiple myeloma, high response rates have been achieved with the VAD regimen in which both VCR (0.4 mg/day × 4) and doxorubicin are administered as continuous infusions along with high dose dexamethasone (Barlogie et al., 1984; Lokhorst et al., 1989; Alexanian et al., 1990; Stenzinger et al., 1990). This regimen may be particularly useful in myeloma complicated by renal failure (Aitchison et al., 1990).

2.4.3.5. *Adult solid malignancies*. Of the adult solid tumors, VCR is most commonly used in combination with other agents in treating small cell carcinoma originating in pulmonary or extrapulmonary sites. Effective regimens for small cell lung cancer containing VCR include CAV (cyclophosphamide, doxorubicin, VCR) which has produced partial and complete remissions in 53% to 63% of patients (Johnson et al., 1987). CAV was one of the most popular regimens until the development of cisplatin–etoposide combinations. Other regimens utilizing VCR include CAV/EP (cycles of CAV alternating with cycles of etoposide and cisplatin), CAVE (cyclophosphamide, doxorubicin, VCR, and etoposide) and CAVVP-16 (cyclophosphamide, doxorubicin, VCR, and etoposide) (Comis et al., 1987; Messieh et al., 1987; Einhorn et al., 1987). Although VCR has not substantially improved the overall therapeutic results of combination chemotherapy in patients with advanced and metastatic non-small cell lung carcinoma (Sorensen et al., 1987), an extraordinarily high objective response rate (66%) has recently been reported with CODE (cyclophosphamide, VCR, doxorubicin, and etoposide), a dose intensive multi-agent regimen (Murray et al., 1991).

VCR administered in combination regimens such as MOF (methyl-CCNU, VCR, 5-fluorouracil) has been evaluated in the metastatic and adjuvant settings in colorectal carcinoma. Enthusiasm for this combination arose from a small randomized comparison study of MOF versus 5-fluorouracil in patients with metastatic disease (Moertel et al., 1975). The objective response rate with MOF was twice that observed with 5-fluorouracil (43% versus 19%), but there were no significant survival differences and subsequent attempts to confirm the superiority of MOF have not been uniformly successful (Macdonald et al., 1976; Kemeny et al., 1979). The initial activity reported with MOF in metastatic disease has influenced its use in the adjuvant setting. MOF was associated with an improved disease-free and overall survival in patients with Dukes B₂ and C rectal carcinoma compared to cohorts randomized to receive observation only or adjuvant radiotherapy (Fisher et al., 1987). Although VCR is active in metastatic breast cancer and is frequently used in combination regimens due to its

lack of myelosuppressive effects, a high incidence of severe neurotoxic events were observed in early phase II single agent trials (Henderson, 1987). VCR has also been incorporated into many active combination regimens in both adjuvant and metastatic settings including CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil, VCR, and prednisone) (Segaloff et al., 1985; Perloff et al., 1986) and a novel 16 week dose intensive regimen consisting of cyclophosphamide, VCR, 5-fluorouracil, methotrexate, and doxorubicin (Abeloff et al., 1990.) However, several randomized trials, including trials comparing CM-FVP to CMFP and the combination of doxorubicin and VCR to doxorubicin alone, have also shown that VCR contributes little or nothing to response rate and overall survival (Steiner et al., 1983; Segaloff et al., 1985). Therefore, VCR is not generally used in conventional first-line regimens in patients with metastatic breast cancer.

Drug combinations containing VCR have demonstrated antitumor activity in patients with bone and soft tissue sarcomas (Mandell et al., 1988; Mauer et al., 1988; Pezzi et al., 1990), advanced and metastatic carcinoma of the cervix (Wheelock et al., 1990), and uterine (Sorbe et al., 1989), vulvar (Shimizu et al., 1990) and head and neck (Recloux et al., 1989) carcinomas, malignant histiocytosis (Sonneveld et al., 1990), choriocarcinoma (Gallion et al., 1989; Pustin et al., 1989) and melanoma (York and Foltz, 1988); however, it is difficult to assess the contribution of VCR in each of these therapies. VCR has also been one of the most active agents used alone or in combination with other drugs (e.g. VBL, etoposide, doxorubicin, and bleomycin) in the palliative therapy of Kaposi's sarcoma associated with the acquired immunosufficiency syndrome due to both its antitumor activity and its relative lack of myelosuppressive effects (Kriegel, 1984; Kaplan et al., 1986; Volberding 1987; Gill et al., 1989, 1990) (see Section 2.5.3, Clinical Applications). VCR has also been incorporated into several multi-agent regimens in gliomas with variable therapeutic results (Lefkowitz et al., 1988; Levin et al., 1990; Longee et al., 1990).

2.4.3.6. *Pediatric solid malignancies.* VCR has frequently been incorporated into combination regimens used in the treatment of many pediatric solid tumors. A review of the experience with single agent VCR in medulloblastoma has revealed that the agent produced objective responses in 11 of 15 patients; however, responses were generally brief (Lassman et al., 1966; Lampkin et al., 1967; Smart et al., 1968; Christ et al., 1976; Levin et al., 1989). Multi-agent regimens employing VCR in combination with other drugs such as CCNU, BCNU, procarbazine, methotrexate, cyclophosphamide, and prednisone have been used in the adjuvant setting as well as in patients with recurrent, progressive, and systemic disease (Duffner et al., 1979; Thomas et al., 1980; Cangir et al., 1984; Friedman et al., 1986; Kretchman

et al., 1989; Evans et al., 1990; Lefkowitz et al., 1990; Tait et al., 1990). Combination regimens that contain VCR have also been demonstrated to be active in advanced and recurrent oligodendrogliomas and ependymomas (Cairncross and Macdonald, 1988; Macdonald et al., 1990), Wilms' tumor (Arrigo et al., 1990; Green, D. M. et al., 1990), neuroblastoma (Bernard et al., 1987; Kushner et al., 1990; Pinkerton et al., 1990), and Ewing's sarcoma (Burgert et al., 1990; Tefft et al., 1990).

2.4.3.7. *Miscellaneous.* Although the majority of these reports are anecdotal, VCR has been demonstrated to be active in several non-malignant hematologic disorders. Infusions of VCR or VCR-loaded platelets have been reported to be effective in some cases of refractory autoimmune thrombocytopenia (Rogers and Ries, 1980; Fenauz et al., 1990), thrombotic thrombocytopenia purpura (Gutterman and Stevenson, 1982; Linares et al., 1988; Welborn et al., 1990), lymphomatoid granulomatosis (Jenkins and Zalonznik, 1989) and hemolytic uremic syndrome (Gutterman et al., 1983). VCR has also been used as an immunosuppressive agent following cardiac transplantation (Crandall et al., 1990) and after factor VIII infusions in patients with acquired factor VIII inhibitor (Lian et al., 1989).

2.4.3.8. *Reversing clinical resistance to VCR.* Recently, there has been considerable interest in using pharmacologic agents to reverse resistance to VCR and other natural products conferred by the mdr phenotype. To date, most trials have used calcium channel antagonists such as verapamil, which have produced significant cardiovascular toxicity at suboptimal concentrations (Bessho et al., 1985; Present et al., 1986; Ozols et al., 1987; Cairo et al., 1989; Fedeli et al., 1989; Dalton et al., 1989; Miller et al., 1991). However, responses have been documented in patients with multiple myeloma and non-Hodgkin's lymphoma receiving calcium channel antagonists in combination with multi-agent regimens like VAD and CVAD (dexamethasone and continuous infusions of VCR and doxorubicin with and without cyclophosphamide) after these identical regimens without calcium channel antagonists were previously shown to be inactive (Dalton et al., 1989). Preliminary studies have also demonstrated that it is possible to achieve therapeutic concentrations of many other classes of agents capable of modulating the mdr phenotype such as phenothiazines and other calmodulin inhibitors, antiestrogens and cyclosporin A (Lum et al., 1991; Yahanda et al., 1991; Erlichman et al., 1991; Kane et al., 1991; Durivage et al., 1991; Trump et al., 1991).

2.4.4. Toxicities

2.4.4.1. *Neurologic.* Peripheral neurotoxicity is the principal dose-limiting toxicity of VCR (Sandler

et al., 1969; Weiden and Wright, 1972; Rosenthal and Kaufman, 1974; Kaplan and Wiernik, 1982; Legha, 1986). Peripheral neurotoxicity is typically cumulative. Initially, only symmetrical sensory impairment and parasthesias may be encountered. However, neuritic pain and motor dysfunction may occur with continued treatment. Loss of deep tendon reflexes, foot and wrist drop, ataxia, and paralysis may also be observed with continued use. These effects are almost always symmetrical and may persist for weeks to months after discontinuing the drug. Patients may also complain of bone, back, limb, and tumor pain. VCR-induced peripheral neuropathic effects usually begin in adults who have received a cumulative dose of 5 to 6 mg and the toxicity may occasionally be profound after a cumulative dose of 15 to 20 mg. Children generally tolerate this toxicity better than adults, and the elderly are particularly susceptible. It has also been felt by some that patients with lymphomas are more predisposed to VCR-induced peripheral neurotoxicity compared to patients with other malignancies (Lane and Routledge, 1983). In addition, severe neuropathic effects have been observed after the administration of VCR to patients with antecedent neurologic disorders such as hereditary motor and sensory neuropathy type I, Charcot-Marie Tooth Disease and childhood poliomyelitis (Griffiths *et al.*, 1985; Miller, 1985; McGuire, S. A., *et al.*, 1989a).

Despite the pathologic findings of axonal degeneration and demyelination, peripheral nerve conduction velocities are generally normal except in patients with severe motor dysfunction. Electrodiagnostic testing has usually revealed diminished amplitudes in sensory and motor nerve action potentials and prolonged distal motor latencies (Bradley *et al.*, 1970; Weiss *et al.*, 1974). In experimental studies, the motor endplate may also be disrupted (Bradley *et al.*, 1970). Unmyelinated fibers may be the most sensitive to the toxic effects of VCR which explains the early loss of deep tendon reflexes (Donoso *et al.*, 1977; Goldstein and Lowndes, 1978). The development of a predictive model for the peripheral neuropathy associated with VCR has been an elusive goal; however, models that appear useful and deserve further attention include dorsal root ganglion cell cultures (Masurovsky *et al.*, 1981a,b, 1983), cerebellar explants (Gilbert *et al.*, 1989) and snail neuron (Muller *et al.*, 1990) and rabbit models (Norido *et al.*, 1988).

VCR may also disrupt motor, sensory, and cranial nerve functions resulting in hoarseness, diplopia, jaw pain, pharyngeal pain, parotid pain, and facial palsy. Alterations in mental status associated with depression, confusion and insomnia have also been reported. Although uptake of both VCR and VBL into the brain has been shown to be very low due to their low cerebrovascular permeability and extensive binding to plasma constituents (Greig *et al.*, 1990; Castle *et al.*, 1976b; Jackson *et al.*, 1980), central

nervous system manifestations of neurotoxicity are occasionally observed. VCR-induced seizures have been reported in association with hypertension, confusion, depression, agitation, insomnia, hallucinations, and coma (Bradley *et al.*, 1970; Kaplan and Wiernik, 1982; Rosenthal and Kaufman, 1974; Hurwitz *et al.*, 1988). However, these effects may also have been due to intracranial metastases, infection, metabolic disturbances or other drugs. Seizures have also been associated with the well-documented ability of VCR to induce the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and hyponatremia which appears to be due to direct drug effects on the hypothalamus, neurohypophyseal tract or posterior pituitary (Stuart *et al.*, 1975; Kaplan and Wiernik, 1982). In addition, visual effects, including transient cortical blindness, retinal changes, and optic atrophy with cortical blindness, have been associated with VCR (Bird *et al.*, 1983; Ripps *et al.*, 1989). VCR has also been temporally associated with a partially reversible hearing loss (Yousif *et al.*, 1990) as well as neurological syndromes characterized by ataxia and athetosis (Carpentieri and Lockhart, 1978). Direct intrathecal injections of the agent have induced a myeloencephalopathy characterized by ascending motor and sensory neuropathies and death (Slyter *et al.*, 1980; Williams *et al.*, 1983; Gaidys *et al.*, 1983; Dyke, 1989).

Acute, severe autonomic effects due to VCR are unusual and generally occur as a consequence of high-dose therapy (greater than 2 mg/m^2) or in patients with hepatic dysfunction. Autonomic effects include paralytic ileus, urinary retention, cardiac autonomic dysfunction, orthostatic hypotension, and arterial hypotension and hypertension (Carmichael *et al.*, 1970; Gottlieb and Cuttner, 1971; Hironen *et al.*, 1989; Lahninen *et al.*, 1989). An acute necrotizing myopathy has also been reported (Blain, 1984).

Possible additive or synergistic effects of other potentially neurotoxic agents such as cisplatin on VCR-induced neurotoxicity have not been adequately characterized. Currently, the only known treatment for neurotoxicity related to VCR is drug discontinuation or the reduction of dose and/or frequency of administration. There have also been numerous attempts to decrease or prevent neurotoxicity with agents such as thiamine, vitamin B12, pyridoxine, and folinic acid (Grush and Morgan, 1979; Thomas *et al.*, 1982; Jackson *et al.*, 1986b,c, 1988), however, these reports have generally been either anecdotal, negative, or inconclusive. Folinic acid, but not folic acid, has been shown to protect mice against an otherwise lethal dose of VCR and has been used in several cases of VCR overdosage in man (Johnson *et al.*, 1963), but reports of its effectiveness as an antidote for VCR toxicity have been conflicting (Grush and Morgan, 1979; Thomas *et al.*, 1982; Dyke, 1989). Concurrent administration of a mixture of gangliosides (Cronassial) with VCR has also been

reported to reduce the peripheral neurotoxicity associated with standard doses of VCR (Helmann et al., 1987). However, the most encouraging agent for prophylaxis of VCR-related neuropathic effects has been glutamic acid based on its ability to enhance microtubule formation *in vitro* (Jackson et al., 1988) and possible competition between VCR and glutamic acid for carrier-mediated transport at the cell membrane level. In a prospective randomized trial, coadministration of glutamic acid to patients receiving VCR has been associated with a significant diminution of neurotoxicity, including reducing effects on the Achilles tendon reflex and less severe paresthesias. However, there have been no evidence that glutamic acid ameliorates either VCR-related gastrointestinal or hematologic effects.

2.4.4.2. *Gastrointestinal.*

Constipation, abdominal cramps, weight loss, nausea, vomiting, oral ulcerations, diarrhea, paralytic ileus, intestinal necrosis and/or perforation, and anorexia may occur after the administration of VCR (Carmichael et al., 1970, Gottlieb and Cuttner, 1971; Kaplan and Wiernik, 1982; Sharma, 1988; Hironen et al., 1989; Lahninen et al., 1989). Constipation may be associated with impaction of stool in the upper colon. Thus, the rectum may be empty on digital examination and an abdominal radiograph may be useful in detecting this condition. This entity may be responsive to high enemas and laxatives. A routine prophylactic regimen against constipation is recommended for all patients receiving VCR. Paralytic ileus may occur, particularly, in pediatric patients. The ileus, which mimics a 'surgical abdomen' will usually abate upon temporary discontinuation of VCR and symptomatic care. Patients who receive high VCR doses and/or have hepatic dysfunction appear to be particularly prone to severe gastrointestinal complications.

Several agents have been used in an attempt to minimize the paralytic ileus produced by VCR. Lactulose (Harris and Jackson, 1972), caerulein (Agosti et al., 1971), metaclopramide (Garewal and Dalton, 1985), and sincalide, a cholecystokinin analog (Jackson et al., 1982), have been used to stimulate bowel motility. Although these anecdotal reports suggest that the drugs may offer some relief of gastrointestinal disturbances, it has been suggested they may also adversely alter the pharmacokinetics of VCR and other vinca alkaloids by altering biliary excretion and/or enterohepatic recirculation which may ultimately reduce their systemic half-lives (Castle, 1989).

2.4.4.3. *Genitourinary.*

VCR may cause bladder atony that can result in polyuria, dysuria, incontinence, and acute urinary retention (Gottlieb and Cuttner, 1971). Therefore, it has been suggested that other drugs that are known to cause urinary retention, particularly in the elderly, should, if possible, be discontinued for several days following the administration of VCR.

2.4.4.4. *Endocrine.*

VCR has been implicated as a cause of the SIADH by directly affecting the hypothalamus, neurohypophyseal tract or posterior pituitary (Stuart et al., 1975; Kaplan and Wiernik, 1982). SIADH may result in symptomatic hyponatremia with seizures, especially in patients receiving intensive hydration. This VCR-induced entity has been associated with elevated serum ADH levels and usually remits within 2 to 3 days after onset. Hyponatremia generally improves with fluid restriction.

2.4.4.5. *Cardiovascular.*

Hypertension and hypotension, presumptively due to VCR-induced autonomic dysfunction, have been observed with VCR (Carmichael et al., 1970; Hironen et al., 1988). There have also been several reports of acute cardiac ischemia, including massive myocardial infarction, following the administration of VCR (Barra et al., 1985; Mandel et al., 1975; Weinstein et al., 1976; Somers et al., 1976; Von Hoff et al., 1982; Kantor et al., 1981). The mechanism for these effects has not been determined.

2.4.4.6. *Hematologic.*

Serious myelosuppression due to VCR is very rare. However, mild to modest anemia, leukopenia, and thrombocytopenia are occasionally observed with conventional doses and schedules. (Steurer et al., 1989). Serious hematologic toxicity has also been a major feature of inadvertent VCR overdosage (Kaufman et al., 1976). VCR may also increase circulating platelets due to the endoreduplication of megakaryocytes (Bunn et al., 1975).

2.4.4.7. *Dermatologic.*

VCR-induced alopecia and rashes occur in approximately 20% of patients. The drug is considerably irritating to dermal tissues and extreme care should be taken to prevent its extravasation into soft tissues. If extravasation is suspected, the infusion should be discontinued. An attempt to aspirate any residual drug remaining in the tissues should also be made. Application of local heat and injection of hyaluronidase 150 mg subcutaneously in a circumferential manner around the needle site are thought to minimize discomfort (Dorr and Alberts, 1985). Corticosteroids have also been used successfully in treating drug extravasations (Bellone, 1981); however, it is not known whether the beneficial effects of corticosteroids are due to non-specific anti-inflammatory properties or to specific inhibitory effects on cytotoxicity (Cutts, 1968).

2.4.4.8. *Miscellaneous.*

Fever without any obvious etiology has occurred after the administration of VCR (Ishii et al., 1988). Pain in tumor tissues may also occur. In addition, severe hepatic toxicity has been reported with VCR used in combination with dactinomycin in patients with Wilms' tumors (Green, D. M., et al., 1990).

2.5. Vinblastine

2.5.1. Clinical Pharmacology

The clinical pharmacology of VBL reflects VBL's extensive tissue binding and resembles that of VCR. Serum protein binding has been reported to range from 43% to 99.7% (Owellen and Hartke, 1975; Owellen et al., 1977a; Steele et al., 1982). VBL also extensively binds to formed blood elements, with 50% of radiolabeled drug bound to platelets, red blood cells, and white blood cells within 20 min after an intravenous injection (Creasey, 1975; Greenius et al., 1968; Hebden et al., 1970). Extensive platelet binding is probably due to the high concentrations of tubulin in platelets.

VBL's plasma disappearance best fits a triexponential model with a rapid distribution phase ($t_{\frac{1}{2}}$alpha < 5 min) due to rapid tissue binding (Owellen and Hartke, 1975). VBL is more avidly sequestered in tissues than VCR as demonstrated by retention of 73% of radioactivity in the body 6 days after an injection of the radiolabeled agent (Owellen and Hartke, 1975). Reported values for beta and gamma $t_{\frac{1}{2}}$ range from 53 to 99 min and 20 to 24 hr, respectively (Owellen and Hartke, 1975; Creasey, 1975; Nelson, 1982). Following intravenous injections of standard doses of VBL, peak plasma concentrations are approximately 0.4 μM (Creasy, 1975; Nelson et al., 1980; Nelson, 1982). Long terminal half-lives and high steady-state concentrations have been reported following continuous intravenous infusions of VBL: 1.1 nM at 1 mg/m^2/day ($t_{\frac{1}{2}}$ = 28 days); 3.3 nM at 1.7 mg/m^2/day ($t_{\frac{1}{2}}$ = 3 days); and 6.6 nM at 2 mg/m^2/day ($t_{\frac{1}{2}}$ = 6 days) (Lu et al., 1979; Young et al., 1984).

VBL is principally excreted in the bile indicating that patients with hepatic excretory insufficiency may be more predisposed to drug toxicities than patients with normal hepatic function (Owellen and Hartke, 1975). Less than 15% of an administered dose of VBL is excreted in the urine, but fecal excretion of the parent compound is also low which suggests that the agent undergoes extensive metabolism. Following administration of radiolabeled VBL to dogs, 30 to 36% of radioactivity has been found in bile and 12 to 17% has been recovered in urine over a 9 day period (Lu et al., 1979). At least 1 metabolite, desacetyl vinblastine (vindesine; VDS), which may be as active as the parent compound, has been identified in both dogs and man (Creasy and Marsh, 1973; Owellen et al., 1977a). Minute quantities of VDS have also been detected in the urine and stool. Although the principal site of VDS formation has not been definitively determined, it appears to be in the liver.

2.5.2. Dose and Schedule

VBL has been administered by several schedules. The most common schedule involves weekly bolus doses of 6 mg/m^2 incorporated into combination chemotherapy regimens such as ABVD (adriamycin, bleomycin, VBL, dacarbazine (Bonadonna et al., 1979; Santoro and Bonadonna, 1979; Santoro et al., 1982a,b; Bonadonna et al., 1986) and the MOPP–AVB 'hybrid' regimen (nitrogen mustard, VCR, prednisone, procarbazine, adriamycin, bleomycin, VBL (Klimo and Connors, 1985a)). The manufacturer recommends starting doses of 2.5 and 3.7 mg/m^2 for children and adults, respectively, followed by gradual dose escalation in increments of approximately 1.8 and 1.25 mg/m^2 per week. Dose escalations should be based on hematologic tolerance. It is also recommended that weekly doses of 18.5 mg/m^2 in adults and 12.5 mg/m^2 in children not be exceeded. However, these doses are substantially higher than most patients can tolerate due to hematologic toxicity, even on less frequent schedules of administration. Since the severity of leukopenia that may occur with identical doses of VBL varies widely, the agent should probably not be given more frequently than once every 7 days.

There are considerable data available pertaining to the administration of VBL on continuous intravenous infusion schedules (Jackson et al., 1990a). The most common continuous infusion schedules have employed VBL infusions for five consecutive days at doses ranging from 1.5 to 2.0 mg/m^2/day (Yap et al., 1980, 1983; Zeffrin et al., 1984; Ratain and Vogelzang, 1986; Jackson et al., 1990a; Von Hoff et al., 1990).

As in the case with VCR, VBL dose modifications should be made for significant liver dysfunction, especially biliary obstruction, due to the importance of the liver and biliary system in drug disposition. However, specific guidelines for dose modifications have not been firmly established (see Section 2.4.2, Vincristine, Dose and Schedule).

2.5.3. Clinical Applications

2.5.3.1. Leukemia. The selection of either VCR or VBL in combination chemotherapy regimens for specific malignancies has not been strictly based on an inherently superior antitumor spectrum for either agent. Instead, it has been largely based on historical grounds and to avoid overlapping toxicities when combined with other classes of agents. For example, VBL has been shown to be modestly active in ALL (Warwick et al., 1960), but it has never been thoroughly evaluated in this disorder, especially on a weekly administration schedule which appears to be VBL's most effective schedule in both solid tumors and lymphomas. Interestingly, activity has been seen with the combination of VBL and VCR in children who were previously demonstrated to be resistant to VCR (Massimo et al., 1969). Although some activity was reported in early clinical trials (Hodes et al., 1962), VBL has been studied even less in AML. At the present time, VBL does not have any role in the therapy of the acute leukemias.

2.5.3.2. *Hodgkin's lymphoma.* In early clinical trials in advanced Hodgkin's disease, VBL was demonstrated to be one of the most active single agents, producing complete and overall responses in 33% and 65% of patients, respectively (Livingston and Carter, 1970). However, the durability of most responses to single agent VBL was limited. Although VCR was incorporated into the first successful and most popular regimen for Hodgkin's disease, MOPP (nitrogen mustard, VCR, prednisone, procarbazine), due to VCR's relative lack of myelosuppressive properties, equivalent antitumor activity has been associated with modified MOPP regimens which employ VBL instead of VCR. The substitution of VBL for VCR in modified MOPP regimens, including BCVPP (BCNU, cyclophosphamide, VBL, procarbazine, prednisone) (Bakemeier *et al.*, 1984); MVPP (nitrogen mustard, VBL, procarbazine, prednisone) (Sutcliffe *et al.*, 1978; Wagstaff *et al.*, 1986); ChlVPP (chlorambucil, VBL, procarbazine, prednisone) (Selby *et al.*, 1990); and CVPP (CCNU, VBL, procarbazine, prednisone) (Diggs *et al.*, 1977), though, has resulted in considerably less neurotoxicity.

Recent attempts to improve on the results achieved with MOPP or modified MOPP regimens in Hodgkin's disease have focused on the development of 'non-cross resistant' drug combinations. The first and most popular of these regimens was ABVD which consisted of VBL along with doxorubicin, bleomycin, and dacarbazine (Papa *et al.*, 1982; Santoro and Bonadonna, 1979; Santoro *et al.*, 1982b). However, ABVD has not conclusively been demonstrated to be superior to MOPP. In comparison trials, however, MOPP has generally been given with individual drugs, including VCR, at reduced doses compared to early trials (Canellos *et al.*, 1988). Excellent therapeutic results have also been reported with regimens utilizing alternating cycles of MOPP and ABVD (MOPP/ABVD) (Santoro *et al.*, 1982a; Bonadonna *et al.*, 1986; Canellos *et al.*, 1988), and with the 'MOPP/ABV hybrid', a variant of MOPP/ABVD in which dacarbazine is omitted and all drugs except prednisone are given in a span of 8 days (Klimo and Connors, 1985a). However, a clear therapeutic superiority of 'non-cross resistant' and more complex alternating regimens over MOPP has not been conclusively demonstrated.

2.5.3.3. *Non-Hodgkin's lymphomas.* Although VBL is clearly active as a single agent in non-Hodgkin's lymphoma (Stutzman and Ezdinli, 1966; Carbone and Spurr, 1968; Livingston and Carter, 1970), VBL has not generally been incorporated into conventional 'first-line' regimens as compared to VCR. Again, this is largely due to historical reasons and VCR's relative lack of overlapping hematologic toxicities. However, combination chemotherapy regimens containing VBL are clearly active and may be useful in first-line and salvage therapies (Palmieri *et al.*, 1990). There is even evidence suggesting a lack of

cross-resistance in VCR-refractory patients (Jackson *et al.*, 1987).

2.5.3.4. *Urologic and germ cell malignancies.* VBL is active as a single agent and is used as an integral component of both curative and palliative treatment regimens for several advanced urological malignancies, particularly germ cell carcinoma, transitional cell carcinoma of the urothelial tract, and renal cell carcinoma.

For gonadal and extragonadal germ cell malignancies, VBL-based regimens, particularly VBL-bleomycin combinations largely developed by Samuels *et al.* (1975, 1976) were the mainstay of treatment until the discovery of cisplatin and its introduction into therapeutic combinations in the mid 1970s. The combination of cisplatin and VBL has been the foundation for several very successful drug regimens which are capable of curing the majority of patients with germ cell malignancies (Loehrer *et al.*, 1988b). The most popular of these regimens has been the combination of cisplatin, VBL, and bleomycin which is commonly known as PVB or the 'Einhorn regimen.' This regimen, developed by Einhorn and colleagues at Indiana University, originally employed VBL at doses of 0.2 mg/kg on day 1 and 2 along with cisplatin (20 mg/m^2/day × 5 days) and bleomycin (30 units weekly) every 3 weeks for 4 courses (Einhorn and Donohue, 1977). Maintenance therapy consisting of VBL (0.3 mg/kg) was also administered monthly for 21 consecutive months (Einhorn *et al.*, 1981). The principal and most serious toxicities of the original PVB regimen, including paralytic ileus, myalgias, peripheral neuropathy, and granulocytopenia, were related to the high-doses of VBL. Therefore, the EORTC and the Indiana University group conducted randomized prospective trials comparing the original regimen (VBL total dose = 0.4 mg/kg/course) to the same regimen but with a 25% reduction in the VBL dose (0.3 mg/kg/course); maintenance VBL was also employed in both treatment arms (Einhorn and Williams, 1980; Stoter *et al.*, 1986). There were no significant differences in the efficacy of the regimens, but there was a significant increase in both hematologic and non-hematologic toxicities with the higher dose of VBL. Subsequent studies have demonstrated that maintenance therapy with VBL is not necessary (Einhorn *et al.*, 1981).

In parallel with the development of PVB at Indiana University was the similar series of regimens (VAB-I to VAB-6) developed at Memorial Sloan-Kettering Cancer Center. Initially, the combination of VBL, bleomycin, and actinomycin-D was the foundation for VAB-1 (Wittes *et al.*, 1976; Cheng *et al.*, 1978); however, the doses and schedules of these agents were later modified, and cisplatin was also added culminating in VAB-6 (Cheng *et al.*, 1978; Bosl *et al.*, 1986). Maintenance therapy with VBL and actinomycin-D was also not found to be useful during the course of VAB-6's development (Bosl *et al.*, 1986). Similar

VBL-based regimens such as PVB have also played an important role in the curative therapy of germ cell malignancies originating in the ovaries (Williams et al., 1989), extragonadal germ cell tumors and advanced poorly differentiated carcinomas of unknown primary sites (Hainsworth et al., 1988). Although VBL-based combination regimens like PVB and VAB-6 have been extremely active in advanced germ cell malignancies, VBL has largely been replaced by etoposide in induction regimens due to the more favorable toxicity profile of etoposide (Williams et al., 1987; Bosl et al., 1988). However, second-line combination therapies using either VBL or VP-16 (etoposide) in combination with ifosfamide, and cisplatin (VIP) have been demonstrated to induce durable complete responses in patients who have relapsed after receiving first-line regimens containing cisplatin and etoposide (Loehrer et al., 1988c).

Major advances in the treatment of transitional cell carcinoma of the urothelial tract have largely focused on combination chemotherapy regimens containing cisplatin and methotrexate (Yagoda, 1986, 1987). The overall response rate of combinations of cisplatin and methotrexate has approached 45%, but both the complete response rate and the durability of responses have been low. Recently, more successful combination regimens have also utilized VBL which has single agent activity of approximately 16% (Yagoda, 1986, 1987). These more intensive multi-drug combinations such as CMV (cisplatin, VBL, methotrexate) and M–VAC (methotrexate, VBL, doxorubicin, and cyclophosphamide) have been reported to induce complete responses in 28% and 37% of patients, respectively (Harker et al., 1985; Sternberg et al., 1988, 1989). In fact, survival durations that are greater than two years have been reported for 78% of complete responders to M–VAC. Although preliminary trials with M–VAC have been encouraging with respect to overall antitumor activity, benefit has primarily been rendered in patients with low disease volumes. Toxicity has also been significant. Studies are currently assessing the benefits of these regimens in the neoadjuvant and adjuvant settings (Scher et al., 1988, 1989; Miller et al., 1990).

Chemotherapy for advanced and metastatic renal cell carcinomas has generally yielded disappointing results; however, the best consistent single agent activity has been with VBL administered at weekly doses of 0.2 to 0.3 mg/kg. Although response rates as high as 31% and markedly prolonged survival for responders have been reported with weekly VBL doses of 0.2 mg/kg (Hrushesky and Murphy, 1977), most studies have utilized lower VBL doses due to drug-related toxicities. These efforts have resulted in response rates ranging from 15% to 30% (Linehan et al., 1989). Continuous infusions of VBL at daily doses ranging from 1.4 to 2.0 mg/m² for 5 consecutive days have also been evaluated, but the antitumor activity associated with prolonged infusions has not

generally been superior to that achieved on bolus schedules, and objective response rates ranging from 0% to 25% have been reported (Elson et al., 1988; Jackson et al., 1990a). In addition, combination chemotherapy regimens containing VBL have not been demonstrated to be superior to single agent VBL. However, response rates with multi-agent therapy have been high in some studies. For example, the combination of VBL, bleomycin, high-dose methotrexate, and leucovorin has been reported to produce objective responses in 30% of patients (Bell et al., 1984). Interesting results have also been achieved with combinations of VBL and biologic agents such as recombinant interferon-alpha (Schornagel et al., 1989; Neidhart et al., 1991). Responses to VBL and interferon-alpha administered on a daily schedule have ranged from 15% to 29%, with complete responses occurring in approximately 5% of patients; however, clinical trials have failed to demonstrate that the combination is superior to either interferon-alpha or VBL alone with the exception of patients with pulmonary metastates as their sole site of metastatic disease (Neidhart et al., 1991).

2.5.3.5. *Breast cancer.* Although VBL is active in breast cancer as a single agent (Giaccone et al., 1988), the agent is not generally incorporated into adjuvant or first-line regimens for metastatic disease since it compounds the myelosuppression due to other active agents. Instead, VBL is more commonly incorporated into secondary and tertiary regimens. Response rates ranging from 45% to 53%, a medium response duration of approximately 1 year and a median survival of 13 to 16 months have been reported with VATH (VBL, doxorubicin, thiotepa, and halotestin) (Perloff et al., 1978; Hart et al., 1981). Another popular regimen for patients failing doxorubicin-based regimens who have an anticipated response rate of approximately 20% to subsequent therapies (Henderson, 1987), is the combination of mitomycin C, 20 mg/m² on day 1, and VBL, 0.5 mg/m² on days 1 and 28 given every 6 to 8 weeks. This regimen has been associated with response rates as high as 40% and median durations of responses of approximately 4 months (Denefrio et al., 1978; Konits et al., 1981; Garewal et al., 1983).

Continuous infusions of VBL have also been associated with intriguing results in metastatic breast cancer. Most trials have employed a daily dose of 1.4 to 2.0 mg/m² for 5 consecutive days in patients who have failed first-line therapies, specifically doxorubicin-based combinations (Yap et al., 1983; Fraschini et al., 1985; Yau et al., 1985; Jackson et al., 1990a). The best results have been reported by Fraschini et al. (1985) who observed 5 complete responses and 34 partial responses among 106 patients, including 5 partial responses in 7 patients who initially failed to respond to VBL given as a bolus injection, and objective responses in 10 out of 22 patients (45%) who previously received VCR. However, there have

been no randomized comparisons evaluating the relative efficacy of bolus versus infusional VBL. Myelosuppression has been the principal toxicity of infusional VBL in heavily-pretreated patients, but the incidences of peripheral neurotoxicity (up to 40%) and gastrointestinal autonomic dysfunction have been high (Shah et al., 1982; Hopkins et al., 1983; Zeffrin et al., 1984; Fraschini et al., 1985).

VBL has been administered by the intrahepatic arterial route in previously-treated breast cancer patients with liver metastases. In a study involving 25 patients receiving intrahepatic VBL (2.0 mg/m^2/day for 5 days), a 36% partial response rate and a median response duration of 5 months (range 3 to 25 months) has been observed (Fraschini et al., 1988b). Hematologic and non-hematologic toxicities have been similar to the adverse effects produced by comparable intravenous doses. These investigators subsequently administered cisplatin 100 mg/m^2 intravenously before intrahepatic VBL. A partial response rate of 33% and severe toxicity were observed (Fraschini et al., 1988a).

2.5.3.6. *Kaposi's sarcoma.* VBL is active alone and in drug combinations in Kaposi's sarcoma associated with the acquired immunodeficiency syndrome (Gill et al., 1989). Due to compromised hematopoietic function in these patients, relatively low starting doses of VBL, 4 mg intravenously on a weekly schedule, have generally been used with gradual dose escalation to maintain the total white blood cell count at approximately 2500/μl. Using this approach with relatively low doses of VBL (range 4 to 8 mgs weekly; median 6 mg), a group at the San Fransisco General Hospital reported objective responses in 10 of 38 patients, with 19 patients achieving stabilization of their disease which may be an important therapeutic goal in this disease (Kriegel, 1984). The median time to response and duration of response were 5 and 19 weeks, respectively. The regimen was well tolerated. VBL has also been studied in Kaposi's sarcoma in combination with other agents, particularly non-myelosuppressive drugs such as VCR and bleomycin. In a study of weekly alternating VBL (0.1 mg/kg) and VCR (2 mg), 43% of patients had either objective responses or disease stabilization (Kaplan et al., 1986). Major adverse effects included neurotoxicity characterized by muscle weakness and mild paresthesias; however, this approach permitted the administration of 86% and 90% planned doses of VBL and VCR, respectively. Encouraging response rates of 62 to 77%, with many other patients achieving disease stabilization, have also been reported with VBL combined with bleomycin with or without methotrexate (Minor and Brayer, 1986; Glaspy et al., 1986; Wernz et al., 1986; Kaplan et al., 1986).

Intralesional VBL has also been active in treating oral Kaposi's sarcoma in patients with the acquired immunodeficiency syndrome (Epstein et al., 1989; Epstein and Scully, 1989).

2.5.3.7. *Miscellaneous.* VBL is active in gestational trophoblastic disease and is commonly incorporated in both first-line and salvage therapies (DuBeshter et al., 1989; Azab et al., 1989). In addition, VBL has been demonstrated to be active in metastatic non-small cell lung cancer and has been incorporated into successful neoadjuvant (Spain, 1988) and adjuvant programs (Dillman et al., 1990). The agent has also been used for metastatic disease in multi-agent regimens such as MVP (mitomycin C, VBL, cisplatin) (Hardy et al., 1989; Green, M. R. et al., 1990). Although objective response rates with MVP have been reported to be as high as 53% (Mason and Catalano, 1980), MVP and other VBL-based regimens have had a minimal impact on the overall survival of patients with advanced non-small cell lung cancer. Antineoplastic activity has also been observed with VBL alone or in multi-agent regimens in gastric (Von Hoff et al., 1990) and vaginal (Kim et al., 1990) carcinomas, the terminal phase of chronic myelogenous leukemia (Gomez and Sokal, 1979), and malignant histiocytosis (Starling et al., 1972); however, these therapies are not commonly used to treat these neoplasms. In addition, the combination of cisplatin, VBL and bleomycin appears to be active against invasive malignant thymoma (Dy et al., 1988; Goldel et al., 1989) and granulosa cell tumors of the ovary (Zambetti et al., 1990).

As is the case with VCR, slow infusions of VBL have been useful in some patients with refractory idiopathic thrombocytopenic purpura (Fenaux et al., 1990).

2.5.3.8. *Modulation of clinical resistance.* Recently, several investigators have concurrently treated patients with the calcium channel blockers verapamil and VBL in an attempt to modulate VBL resistance attributed to the multi-drug resistant (mdr) phenotype (Bessho et al., 1985; Present et al., 1986; Ozols et al., 1987; Cairo et al., 1989; Fedeli et al., 1989; Dalton et al., 1989; Miller et al., 1991). These attempts have not been altogether successful, which may have been partially due to the inability to achieve optimal plasma levels of verapamil due to cardiovascular effects. Preliminary phase I and pharmacologic trials of VBL and other modulating agents of mdr such as tamoxifen and cyclosporin A have been very encouraging in that optimal *in vitro* concentrations of these modulating agents can be achieved in patients without significant toxicity (Lum et al., 1991; Yahanda et al., 1991; Erlichman et al., 1991; Kane et al., 1991; Durivage et al., 1991; Trump et al., 1991).

2.5.4. *Toxicities*

2.5.4.1. *Hematologic.* Myelosuppression, in particular neutropenia, is the principal toxicity of VBL. Thrombocytopenia and anemia are uncommon.

Nadir blood counts usually occur in 4 to 10 days with recovery by days 7 to 21 post-treatment.

2.5.4.2. *Gastrointestinal.* Mucositis, pharyngitis, and stomatitis are more common with VBL than VCR. VBL may also infrequently cause nausea, vomiting, anorexia, pain, diarrhea, and hemorrhagic enterocolitis. Other gastrointestinal effects that are probably due to autonomic neurotoxicity include constipation, ileus, and abdominal pain. These effects appear to be more common when high VBL doses (>20 mg) are used and when VBL is combined with cisplatin in regimens such as PVB for germ cell malignancies (Bostrom, 1988; Hansen, 1990).

2.5.4.3. *Neurologic.* Neurotoxicity occurs much less commonly with VBL than VCR and is generally observed in patients who have received protracted therapy. The neurotoxic manifestations of VBL are qualitatively similar to those induced by VCR. VBL primarily induces a peripheral neuropathy characterized by sensory dysfunction and loss of deep tendon reflexes. Neurosensory and autonomic effects appear to be more common in heavily-pretreated patients and when VBL is administered by a continuous infusion or in cisplatin-based multi agent combinations such as PVB (Bostrom, 1988; Hansen et al., 1989; Hansen, 1990). Other adverse neurologic effects include mental depression, headaches, parotid gland pain, jaw pain, weakness, bone pain, adynamic ileus, urinary retention, orthostatic hypotension, ataxia, neuromyopathy, vocal cord paralysis and convulsions.

Seizures associated with reduced plasma phenytoin concentrations by 50% have been observed during treatment with VBL and with other vinca alkaloids (Bolin et al., 1983; Jarosinksi et al., 1988). Reduced phenytoin levels have been noted within 24 hr of VCR treatment and levels have been found to be low for up to 10 days.

2.5.4.4. *Cardiovascular.* Hypertension is the most common cardiovascular toxicity of VBL. Sudden and massive myocardial infarctions and cerebrovascular events have also been associated with the use of single agent VBL and multi-agent regimens containing VBL, cisplatin and bleomycin (PVB) (Lejonc et al., 1980; Subar and Muggia, 1986; Kantor et al., 1981; Haris and Wong, 1981). In addition, Raynaud's phenomenon has been a lingering toxicity of VBL combined with cisplatin and bleomycin (Teutch et al., 1977; Hantel et al., 1988; Hansen and Disen, 1989). In one long-term follow-up study of patients who received PVB for germ cell malignancies, symptomatic Raynaud's phenomenon developed in 44% of patients; however, an even higher percentage developed abnormal vasoconstrictive responses to cold stimuli (Hansen and Disen, 1989). This effect did not appear to occur as often when etoposide was substituted for VBL (Williams et al., 1987). Calcium

channel-blocking agents such as nifedipine have been reported to ameliorate symptoms of VBL-induced Raynaud's phenomenon, but the utility of these agents have not been evaluated prospectively (Hantel et al., 1988).

2.5.4.5. *Pulmonary.* Acute pulmonary edema has been observed after the administration of VBL (Israel and Olson, 1978). Acute bronchospasm, acute respiratory distress, interstial pulmonary infiltrates, and dyspnea have also been noted, particularly when VBL is used in combination with mitomycin C (Dyke, 1984; Konits et al., 1981; Ballen and Weiss, 1988).

2.5.4.6. *Dermatologic.* Mild and reversible alopecia is commonly observed with VBL. VBL may also cause photosensitivity reactions and severe irritation in local tissues including the cornea as a consequence of either venous extravasation or local contact. Many antidotes have been recommended for VBL extravasations including corticosteroids (Bellone, 1981), diethylstilbesterol (Cutts, 1968) and hyaluronidase (Dorr and Alberts, 1985), as well as a generally conservative approach (Tsavaris et al., 1990).

2.5.4.7. *Endocrine.* SIADH, which is similar to the syndrome which is more commonly associated with VCR, has been reported to occur with VBL (Ginsberg et al., 1978; Antony et al., 1980).

2.5.4.8. *Miscellaneous.* Pain in tumor-containing tissues has occurred.

2.6. VINDESINE

2.6.1. *Clinical Pharmacology*

After administration of VDS by a bolus intravenous injection, VDS's plasma disposition is characterized by triexponential pharmacokinetics (Nelson, 1982; Nelson et al., 1979, 1980; Owellen and Hartke 1975; Owellen et al., 1977a; Dyke and Nelson, 1977; Hande et al., 1980; Jackson et al., 1984d). VDS is rapidly distributed to body tissues and its alpha $t_{\frac{1}{2}}$ is less than 5 min. Beta and gamma $t_{\frac{1}{2}}$ values have ranged from 55 to 99 min and 20 to 24 hr, respectively. VDS's elimination profile is very long suggesting that drug accumulation may occur with short interval, repetitive dosing schedules. VDS's large volumes of distribution, low renal clearance, and long terminal $t_{\frac{1}{2}}$ also suggests that the agent undergoes extensive tissue binding and delayed elimination. Peak serum VDS concentrations in the range of $0.1\,\mu M$ to $1.0\,\mu M$ are achieved with bolus injections; however, levels typically decrease to less than $0.1\,\mu M$ by 1 to 2 hr. Plasma levels achieved with bolus injection have been reported to be 16-fold higher than levels achieved with prolonged infusion (Ohnuma et al., 1985a). However, optimal AUC and steady-state VDS levels ($0.01\,\mu M$ to $0.1\,\mu M$) have been

achieved with continuous infusion schedules (1.2 to 2.0 mg/m²/day for 2 to 5 days) (Sklaroff et al., 1979; Jackson et al., 1984a; Ohnuma et al., 1985a; Rahmani et al., 1985).

The liver is the principal organ involved in the disposition of VDS (Culp et al., 1977; Hande et al., 1980; Rahmani et al., 1990). In a patient with an external biliary drainage catheter receiving VDS, renal clearance was reported to be low (12 ml/min), but biliary clearance was 29 ml/min, and VDS concentrations in bile were much higher than simultaneously measured plasma levels (Hande et al., 1980). Only 1 to 12% of VDS was measured in the urine of patients receiving the agent on both bolus and infusional schedules (Jackson et al., 1984a; Rahmani et al., 1984).

2.6.2. Dose and Schedule

VDS has been administered on many schedules including weekly and biweekly intravenous bolus and protracted continuous infusional schedules. The agent has also been given in fractionated doses as either an intermittent or a continuous infusion over 1 to 5 days. VDS is most commonly administered as a single intravenous dose of 3 to 4 mg/m² every 7 to 14 days which has been associated with both antitumor activity and tolerable toxicity (Gralla et al., 1979, 1981). Intermittent or continuous infusion schedules generally employ VDS doses of 1 to 2 mg/m²/day for 1 to 2 days or approximately 1.2 mg/m²/day for 5 days every 3 to 4 week (Dyke and Nelson, 1977; Owellen et al., 1977a; Wong et al., 1977; Currie et al., 1978; Mathe et al., 1978; Smith et al., 1978; Bayssas et al., 1979; Gralla et al., 1979; Sklaroff et al., 1979; Bodey et al., 1981; Dirks et al., 1981; Poplin et al., 1983; Yap et al., 1983; Wagstaff et al., 1983; Hansen and Brincker, 1984; Jackson et al., 1984d; DiBella et al., 1984; Ohnuma et al., 1985a; Yau et al., 1985; Mayol et al., 1984; Bezwoda et al., 1984). Longer VDS infusions (up to 21 days) have also been evaluated (de Vries et al., 1989).

Although firm dose modifications have not been established for VDS in patients with hepatic or renal dysfunction, VDS's pharmacologic similarities to other vinca alkaloids and the increased toxicity of VDS in patients with abnormal liver function (Ohnuma et al., 1980) dictate that dose reductions be considered for patients with severe hepatic dysfunction, especially biliary obstruction (see Section 2.4, VCR, for guidelines). There are no data supporting dose reductions in patients with renal dysfunction.

2.6.3. Clinical Trials

VDS is active in a broad range of adult and pediatric malignancies; however a unique role for VDS in oncologic therapeutics has not yet been clearly defined. For this reason, VDS is available only for investigational purposes. Major interest in VDS has been due to its activity in tumors that are refractory to other vinca alkaloids which has suggested a lack of total cross-resistance (Bodey and Freireich, 1976; Dyke and Nelson, 1977; Currie et al., 1978; Mathe et al., 1978; Ohnuma et al., 1978; Smith et al., 1978; Owellen et al., 1977a; Ettinger et al., 1982; Bodey et al., 1980; Valdivieso, 1980; Bayssas et al., 1979; Retsas et al., 1979; Miller et al., 1980; Sordillo et al., 1980; Krivit et al., 1980); however, this has not been demonstrated prospectively in rigorous studies.

2.6.3.1. Non-small cell lung cancer. VDS is not currently used in the standard therapy of any specific malignancy. It has been most extensively evaluated in metastatic and advanced non-small cell lung cancer. In several comprehensive reviews on the use of vinca alkaloids in non-small cell lung cancer, the cumulative single agent response rate has been reported to range from 15% to 19% (Bakowski and Crouch, 1983; Joss et al., 1984; Sorensen et al., 1987) which is similar to the activity reported for either VCR and VBL (Kris et al., 1985a; Sorensen et al., 1987). However, more substantial single agent phase II data are available for VDS than for either VCR or VBL. In nonrandomized studies of VDS in combination with either mitomycin C or cisplatin, overall response rates have been 36% and 35%, respectively (Gralla, 1985; Kris et al., 1985c). These results are comparable to response rates reported with VBL-based combinations in nonrandomized trials (Sorensen et al., 1987). Other extensively evaluated regimens for non-small cell lung cancer containing VDS include: VDS/ifosfamide (Drings, 1989), VDS/mitomycin C/ifosfamide/cisplatin (Honda et al., 1990), VDS/ifosfamide/cisplatin (Rosell et al., 1990), VDS/mitomycin C/cisplatin (Joss et al., 1990; Rosell et al., 1990), VDS/cisplatin/VP-16 (Klatersky et al., 1983; Albain et al., 1984; Bitran et al., 1986; Ruckdeschel et al., 1986), VDS/cisplatin/cyclophosphamide (Kelsen et al., 1982), VDS/cisplatin/cyclophosphamide/doxorubicin (Kelsen et al., 1982), VDS/methotrexate/cyclophosphamide (Focan et al., 1981), VDS/5-fluorouracil/mitomycin C (Miller et al., 1982), VDS/cisplatin/bleomycin (Itri et al., 1983), VDS/cisplatin/CCNU/cyclophosphamide (Le Chevalier et al., 1985).

While many trials have suggested that the combination of VDS and cisplatin is more active than other drug combinations (Elliot et al., 1984; Shinkai et al., 1985; Niitamo-Korhonen et al., 1989), most randomized trials have failed to confirm that the combination is superior (Gralla et al., 1981; Holsti and Mattson, 1981; Hong et al., 1981; Briancon et al., 1983; Dhingra et al., 1985; Kris et al., 1985b; Ruckdeschel et al., 1986; Hainsworth et al., 1989; Tourani et al., 1989; Luedke et al., 1990; Rosell et al., 1990). In fact, statistically significant differences in response rates have been achieved in only a few studies including a single trial of VDS/cisplatin versus VDS/mitomycin C (43% versus 10%) (Shinkai et al., 1985); a trial of

VDS versus VDS/mitomycin C versus VDS/cisplatin ($<1\%$ versus 27% versus 19%) (Luedke et al., 1990); and a trial of VDS and cisplatin versus single agent VDS (33% versus 7%). This latter trial was the only trial with a statistically significant survival advantage (median survival of 44 weeks for the VDS/cisplatin versus 16 weeks for VDS) (Elliot et al., 1984). Interestingly, response rates have been similar for patients with non-small cell lung cancer randomized between VDS/cisplatin and VBL/cisplatin (17% versus 20%) (Kris et al., 1985b).

Studies of patients with non-small cell lung cancer randomized between the combination of VDS and cisplatin, which was selected as 'state of the art' chemotherapy, and supportive care have also been conflicting. In a Canadian NCI study that randomized patients between the 'best supportive care' and chemotherapy with either VDS/cisplatin or CAP (cyclophosphamide, doxorubicin, and cisplatin), toxicity was substantial for patients receiving chemotherapy; however, the median survival of the supportive-care group was 17 weeks compared to 23 for CAP and 31 for VDS/cisplatin, the latter being a significant improvement (Rapp et al., 1987). In two other studies, patients were randomized to receive either supportive care or the same supportive care plus VDS/cisplatin (Ganz et al., 1987; Woods et al., 1990). In one trial, the median survival with supportive care was 14 weeks which was not significantly different from 20 weeks for the group receiving chemotherapy plus supportive care (Ganz et al., 1987). In another study, the overall response rate to chemotherapy was 28% but there was no significant differences in overall survival between untreated and treated patients (Woods et al., 1990). To date, neither adjuvant nor neoadjuvant studies of chemotherapy combinations containing VDS have consistently supported a unique role for VDS in the treatment of non-small lung cancer (Johnson et al., 1990; Dautzenberg et al., 1990; Vokes et al., 1989).

2.6.3.2. *Miscellaneous.* VDS has also demonstrated activity in ALL (Bayssas et al., 1979; Henderson et al., 1990), blast crisis of CML (Bayssas et al., 1979), and both Hodgkin's (Miller et al., 1980; Lennard et al., 1989) and non-Hodgkin's lymphomas (Bayssas et al., 1979; Coiffier et al., 1989). Responses in leukemia and lymphoma patients who have not responded or relapsed after receiving combination chemotherapy that included VBL or VCR, suggest a lack of complete cross-resistance between VDS and other vinca alkaloids (Mathe et al., 1978; Smith et al., 1978; Bodey et al., 1980; Ettinger et al., 1982; Valdivieso, et al., 1980; Ohnuma et al., 1978; Mathe et al., 1978; Bayssas et al., 1979; Bodey et al., 1980; Miller et al., 1980; Krivit et al., 1980; Lennard et al., 1989; Coiffier et al., 1989).

Combination regimens containing VDS have been active in metastatic and advanced solid tumors such as breast (Smith et al., 1978; Miller et al., 1980;

Walker et al., 1982; Hansen and Brincker, 1984; Yau et al., 1985; Lyss et al., 1989; Falkson et al., 1988), esophageal (Vildivieso, 1980; Lizuka et al., 1990), colorectal (Valdivieso, 1980), head and neck (Tellez-Bernal et al., 1990), and renal carcinomas (Bodey et al., 1981; Wong et al., 1977; Lupera et al., 1989), malignant melanoma (Retsas et al., 1979; Bodey et al., 1981; Valdivieso, 1980; Lakhani et al., 1990; Ringborg et al., 1990; Pectasides et al., 1989; Mulder et al., 1989; Verschraegen et al., 1988), prostate (Cervellino et al., 1990), adenocarcinoma of unknown primary (Kambhu et al., 1990), and pediatric solid tumors (Ettinger et al., 1982), as well as in the neoadjuvant and adjuvant setting in esophageal carcinoma (Bezwoda et al., 1984; Kelsen et al., 1990; Roth et al., 1988). However, these regimens have failed to demonstrate either substantially improved response rates or survival compared to regimens that do not contain VDS. Results of phase II trials in gliomas have also been disappointing (Alavi et al., 1989). In addition, randomized trials of doxorubicin versus doxorubicin and VDS in both soft tissue sarcoma and medullary thyroid carcinoma have failed to demonstrate that the multi-agent combinations containing VDS are superior (Borden et al., 1990; Scherubi et al., 1990).

2.6.4. *Toxicities*

VDS exhibits varying degrees of the toxicities shared by VCR and VBL. Principal dose-limiting toxicities are hematologic and neurologic. These adverse effects are more profound in patients with pre-existing hepatic dysfunction (Ohnuma et al., 1985a).

2.6.4.1. *Hematologic.* Leukopenia is the principal dose-limiting toxicity of VDS, with nadir ANCs occurring in approximately 7 days and recovery within 14 days after bolus injections. Nadir ANCs are observed in approximately 11 to 13 days and recover in 16 to 18 days after continuous infusions given over 5 consecutive days (Bodey et al., 1980; Hande et al., 1980; Valdivieso, 1980; Dyke and Nelson, 1977; Wong et al., 1977; Currie et al., 1978; Mathe et al., 1978). Thrombocytopenia is less severe than leukopenia, with platelet count depressions and recovery occurring in a similar pattern to that of leukocytes. Hematologic toxicity has been demonstrated to correlate best with the rate of VDS elimination and not with peak drug levels (Ohnuma et al., 1985a). Ineffective erythropoiesis and thrombocytosis have also been described (Jumean et al., 1979).

2.6.4.2. *Neurologic.* Neurotoxic effects, characterized by a peripheral neuropathy similar to that described for VCR, are generally observed after 3 to 4 courses (Dyke and Nelson, 1977; Bayssas et al., 1980; Bodey et al., 1980; Ohnuma et al., 1980; Valdivieso, 1980). Neurologic effects are primarily sensory, but motor

dysfunction may also occur (Ohnuma et al., 1978; Bodey et al., 1980; Valdevieso, 1980). Constipation, paralytic ileus, urinary retention, postural hypotension, myalgias, vertigo, and jaw pain occur less frequently (Dyke and Nelson, 1977; Wong et al., 1977; Blum and Dawson, 1976; Tan et al., 1977; Ohnuma et al., 1985a; Currie et al., 1978; Mathe et al., 1978; Smith et al., 1978; Bodey et al., 1980; Valdivieso, 1980; Kanoh, 1989). Obrist and co-workers carefully evaluated neurologic exams and electrophysiological findings in patients receiving VDS at weekly doses of 0.5 to 3.0 mg/m² and found that the only noticeable change was a diminution of proprioceptive reflexes in the lower extremities with attendant diminution of the ankle jerk reflex (Obrist et al., 1979). Central nervous system effects, including cortical blindness, hemiplegia, and disorientation, have also been reported (Heran et al., 1990). Accidental intrathecal administration of the agent has caused death which was preceded by progressive weakness, lethargy diploplia, and ascending paralysis (Robbins, 1985).

2.6.4.3. *Gastrointestinal.* Stomatitis, mucositis, nausea and vomiting may also occur (Tan et al., 1977; Currie et al., 1978; Mathe et al., 1978; Smith et al., 1978; Yau et al., 1985; Hansen and Brincker, 1984; Bodey et al., 1980; Valdivieso, 1980; Amoroso et al., 1989). Gastrointestinal toxicity due to autonomic dysfunction (e.g. constipation and paralytic ileus) have also been observed (Dyke and Nelson, 1977; Wong et al., 1977; Currie et al., 1978; Mathe et al., 1978; Smith et al., 1978; Hansen and Brincker, 1984; Bodey et al., 1980; Valdivieso, 1980; Kanoh, 1989). Diarrhea has rarely been reported (Valdivieso, 1980).

2.6.4.4. *Dermatologic.* Alopecia has been reported with VDS (Hande et al., 1980; Bodey et al., 1980; Valdivieso, 1980; Amoroso et al., 1989). Skin rashes have also been noted in a small proportion of patients (Tan et al., 1977; Currie et al., 1978; Mathe et al., 1978; Smith et al., 1978). As with the other vinca alkaloids, VDS is a potent vesicant, and care must be taken to avoid extravasation into subcutaneous tissues during administration.

2.6.4.5. *Miscellaneous.* Fever, lethargy, cellulitis, and phlebitis have been infrequently noted to occur with VDS (Jackson et al., 1984d; Dirks et al., 1981; Poplin et al., 1983; Hansen and Brincker 1984; Mayol et al., 1984; Valdivieso, 1980; Miller et al., 1980). A high incidence (27%) of local tissue reactions at the injection site without apparent infiltration of the drug has been described (Miller et al., 1980). These reactions may be prevented by flushing the infusion devices with 5% dextrose in water before and after VDS administration (Miller et al., 1980). SIADH has also been observed (Heran et al., 1990). Dyspnea associated with a normal lung scan, electrocardiogram and other diagnostic tests has occurred 1 to 5 hr after the administration of VDS used in combination with mitomycin C (Kris et al., 1984).

2.7. VINORELBINE (NAVELBINE)

2.7.1. Preclinical

Navelbine (NVB; vinorelbine ditartrate; 5'noranhydrovinblastine), a unique semi-synthetic analogue of VBL synthesized by Dr. P. Potier in the late 1970s from catharanthine and vindoline extracted from vinca rosea leaves, is the only vinca alkaloid in clinical use with structural modifications in the catharanthine ring (Potier, 1989). The structure of NVB is shown in Fig. 2. Like the other vinca alkaloids, NVB induces cytotoxicity by inhibiting microtubule assembly; however, NVB appears to be more specific in that it preferentially affects microtubules of the mitotic spindle (Binet et al., 1989; Fellous et al., 1989). In intact tectal plate microtubules from mouse embryos, NVB, VCR, and VBL inhibit mitotic microtubule formation at the same concentration (2.0 μM), and induce cell cycle blockade in metaphase (Binet et al., 1989). At higher concentrations (25 μM), NVB is the only agent that induces blockade in prophase. More importantly, VCR depolymerizes axonal microtubules at concentrations of 5 μM, while VBL and NVB do not induce this effect below 30 μM and 40 μM, respectively, indicating that the latter agents may have a reduced potential for causing neurotoxicity (Binet et al., 1989, 1990).

NVB is active in murine tumor models that are known to be sensitive to other vinca alkaloids such as P388 and L1210 leukemias and M5076 reticulosarcoma, B16 melanoma, producing high T/C ratios (median survival of treated/untreated controls) and many cures (Cros et al., 1989). NVB is also exceptionally active when injected subcutaneously against B16 melanoma, a particularly insensitive murine tumor model. In addition, NVB is active against several human tumor xenografts including non-small cell lung cancer (N6, QG-56, and L-27), small cell lung (LX-1, QG-90, LC-06), breast (MX-1), and gastric (ST-4 and ST-40) carcinomas, and it has been the
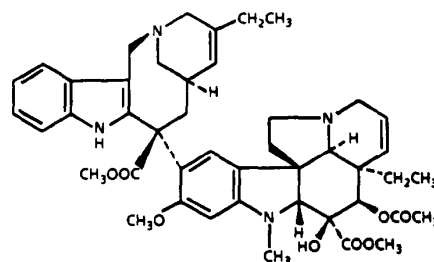

FIG. 2. Structure of Navelbine.

most active vinca alkaloid against human non-small cell lung and one human small cell lung carcinoma xenografts in preclinical studies (Cros *et al.*, 1989). NVB also possesses substantial activity against some very insensitive human tumor xenografts such as L-27 non-small cell lung and ST-4 gastric carcinomas (Cros *et al.*, 1989).

2.7.2. Clinical Pharmacology

The pharmacokinetic behaviour of NVB in rats, monkeys and humans is similar to that of other vinca alkaloids. Drug disposition in plasma has been described by both 2 and 3 compartment models (Rahmani *et al.*, 1984, 1987; Krikorian *et al.*, 1989; Bore *et al.*, 1987; Jehl *et al.*, 1990, 1991). An extensive decay of initial concentrations is observed within the first hour, followed by a slow elimination phase. Consequently, NVB's plasma clearance is quite high (0.4 to 1.29 l/hr/kg), its steady-state volume of distribution is large (25 to 75.6 l/kg), and it has a long elimination half-life (20 to 49 hr) (Rahmani *et al.*, 1987; Krikorian *et al.*, 1989; Bore *et al.*, 1987; Jehl *et al.*, 1990, 1991). In one study, the plasma disappearance of ^{3}H-NVB was modeled in 3 patients; mean alpha, beta, and gamma $t_{\frac{1}{2}}$s were 5.9 min, 155 min, and 50 hr, respectively (Rahmani *et al.*, 1987). Similarly, Jehl *et al.* calculated alpha, beta, and gamma $t_{\frac{1}{2}}$ of 8.4 min, 168 min, and 42.1 hr using HPLC (Jehl *et al.*, 1991). Whereas 80% of ^{3}H-NVB is bound to plasma proteins within the first 2 hr after an intravenous bolus, this percentage decreases to about 50% at 96 hr (Bore *et al.*, 1987). Initially, concentrations of NVB in red blood cells are higher than in plasma, but levels decay faster in red blood cells so that the plasma/red blood cell NVB ratio is approximately 2 after 2 hr (Bore *et al.*, 1987).

Tissue distribution studies in several animal species have shown that high NVB levels are found in several tissues (tissue/plasma ratios of 20 to 80), except in brain and that high levels are sustained for relatively long durations (>5 days in monkeys) (Krikorian *et al.*, 1989). NVB's distribution in tissues, except for fatty tissues, is more intense compared with other vinca alkaloids. Interestingly, NVB concentrations in lung tissue are 3.4- and 13.8-fold higher than VDS and VCR, respectively. Like other vinca alkaloids, the principal route of excretion for ^{3}H-NVB in animals and humans, is in the feces (70% to 80%), while radioactivity found in the urine represents only 20% to 30% of total elimination (Bore *et al.*, 1987; Krikorian *et al.*, 1989). Using HPLC, Jehl *et al.* (1991) have recently determined that urinary excretion of NVB represents only 11% of infused dose. Fecal excretion is extremely slow(>3 to 4 weeks in monkey and humans) and urinary excretion is relatively fast (>50% within 24 hr); however, recovery has been incomplete even after prolonged collections reaching approximately 80% of total dose (Bore *et al.*, 1987) which is similar to incomplete recoveries reported

with other vinca alkaloids (Nelson *et al.*, 1980; Owellen *et al.*, 1977a,b; Rahmani *et al.*, 1986). The primary metabolic fate of NVB has not been definitively determined; however, investigations using animals and human hepatocyte suspensions have strongly suggested that the liver is the principal site of drug disposition excreting large quantities of both NVB and metabolites (Bore *et al.*, 1987; Krikorian *et al.*, 1989). Although the structures of all metabolites have not been identified, comparison of radiochromatograms of extracellular supernatants with standards shows that 2 metabolic peaks are eluted with retention times similar to deacetyl-NVB and an *N*-oxy derivative (Bore *et al.*, 1987). A deacetylated metabolite along with two other unidentified metabolites have been found in human urine, while no metabolites have been detected in serum (Jehl *et al.*, 1990, 1991).

Preclinical pharmacological studies have demonstrated that NVB is also active when given orally. Animal studies have shown that 100% of total radioactivity is absorbed after ingestion of ^{3}H-NVB, while both animal and human studies of a powder filled capsule have shown that the bioavailability of the parent compound is fairly reproducible at 43% (Armand and Marty, 1989; Favre *et al.*, 1989). In humans, peak plasma levels have been achieved within 1 to 2 hr after an oral dose, and erratically high plasma levels have not been observed indicating that the oral route may be a feasible mode of administration. Pharmacologic and bioavailability studies with a liquid filled, soft gelatin capsule have begun.

2.7.3. Dose and Schedule

To date, weekly administration schedules have been evaluated extensively due to NVB's pharmacologic and toxicologic profiles. Both phase I and II studies have verified that weekly NVB doses of 30 mg/m^2 given intravenously and 100 to 130 mg/m^2 given orally are safe (Besenval *et al.*, 1989; Armand and Marty, 1989; Canobibo *et al.*, 1989; Fumoleau *et al.*, 1990; George *et al.*, 1989; Rahmani *et al.*, 1989; Depierre *et al.*, 1991). Leukopenia has been the principal dose-limiting toxicity of NVB given by both routes. Trials evaluating other schedules such as low-dose continuous oral and intermittent high-dose schedules with or without concurrent hematopoietic growth factors are being considered (Armand and Marty, 1989).

2.7.4. Clinical Trials

NVB is only available for investigational purposes in the United States. To date, NVB has demonstrated antitumor activity in advanced breast and non-small cell lung carcinomas in Europe which have generated considerable enthusiasm; however, broad phase II trials have not yet been performed.

2.7.4.1. *Breast cancer.* In the first study of NVB in advanced breast carcinoma, 30 mg/m^2 was administered intravenously on a weekly schedule. The agent induced 5 complete and 6 partial responses in 24 evaluable patients, including 15 patients who received either previous adjuvant or palliative chemotherapy (complete and overall response rates of 21% and 46%, respectively) (Canobibo *et al.*, 1989). The median duration of response was 22 weeks (range, 9 to 41). A particularly high degree of activity occurred in metastases to soft tissue (93% response) and viscera (lung and liver) (50% response). The French NVB study group subsequently reported their collective experience involving 130 fully evaluable patients, 43% of whom had received adjuvant chemotherapy (Delozier *et al.*, 1990; Fumoleau *et al.*, 1990). In this study, NVB given on an identical schedule induced complete and overall responses in 8.5% and 45% of patients, respectively. In another trial involving more heavily pretreated patients with metastatic disease, 2 complete and 7 partial responses occurred out of 38 evaluable patients (overall response rate, 24%) (Tresca *et al.*, 1990). Although the precise activity of oral NVB in advanced breast cancer has not yet been determined in phase II trials, 5 partial and 1 minor responses were noted out of 10 heavily pretreated patients who received oral NVB in a phase I study (Favre *et al.*, 1989).

Extraordinarily high response rates with NVB combined with either doxorubicin or 5-fluorouracil have also been reported in untreated patients with advanced breast carcinoma. The combination of NVB (30 mg/m^2 given intravenously on days 1 and 8 every 21 days) and doxorubicin (50 mg/m^2 on day 1) was associated with complete and overall responses in 24% and 89% of patients, respectively (Spielman *et al.*, 1990). Similarly, NVB (30 mg/m^2 given intravenously on day 1 every 21 days) was administered in combination with 5-fluorouracil (750 mg/m^2 IV days 1 and 5). Of 27 total patients, 9 and 10 experienced complete (33%) and partial (37%) responses, respectively (Dieras *et al.*, 1990). Reversible neutropenia was the major toxicity of both regimens.

2.7.4.2. *Lung cancer.* Exciting results have also been reported with NVB in non-small carcinoma of the lung. Twenty-three of 69 (33%) evaluable patients with advanced disease experienced objective responses after receiving NVB 30 mg/m^2 intravenously on a weekly schedule (Depierre *et al.*, 1991). The median response duration was 34 weeks. Severe leukopenia (WHO grades 3 and 4) occurred in only 12.5% of courses and thrombocytopenia was not observed. Other toxicities included constipation (40%), alopecia (25%), nausea and vomiting (20%), paresthesisas (6.5%), and paralytic ileus (1.3%).

2.7.4.3. *Ovarian cancer.* In a trial involving 32 evaluable, heavily-pretreated patients with ovarian epi-

thelial malignancies, 1 complete and 5 partial responses were observed (overall response rate, 15%) after treatment with NVB 30 mg/m^2 given intravenously on a weekly schedule (George *et al.*, 1989). Three of the 6 responders had previously relapsed on standard therapies. The complete response lasted 73 weeks and the durations of the partial responses ranged from 10 to 47 weeks. Granulocytopenia was severe (WHO grades 3 and 4) in 24% of courses, but this was not surprising considering the extent of previous therapies. Paresthesias were reported in only 23% of patients despite all patients having received prior platinum-based chemotherapy and a significant proportion having received hexamethamelamine. On the other hand, constipation occurred in 52% and was severe in 14%; however, it was felt that much of the constipation was related to extensive intra-abdominal carcinomatosis.

2.7.5. *Toxicities*

2.7.5.1. *Hematologic.* Leukopenia, principally neutropenia, has been the most common adverse effect of NVB. Neutropenia has been dose-limiting with all routes of administration. In a phase I study, intravenous administration of NVB (30 mg/m^2) on a weekly schedule resulted in WHO Grades 3 and 4 neutropenia in 12% and 3% of courses, respectively (Besenval *et al.*, 1989). Similar results have been reported with this schedule in phase II trials (Besenval *et al.*, 1989). The average time of onset for neutropenia has been between 7 and 8 days posttreatment with an average recovery by day 15 to 17. Hematologic toxicity has not been cumulative. It has also been readily reversible soon after the discontinuation of therapy. Treatment delays due to unresolved neutropenia have occasionally been required during phase II studies in non-small cell lung, breast, and ovarian carcinomas; however, two thirds of all injections have been given with a 7-day interval between treatments and treatment delays greater than 1 week have rarely been required even in heavily-pretreated patients (Besenval *et al.*, 1989). Anemia and thrombocytopenia have been rare but asymptomatic thrombocytosis has been fairly common.

2.7.5.2. *Neurologic.* Mild to moderate constipation and a cumulative loss of deep tendon reflexes are the most common neurotoxic manifestations of NVB. Paresthesias, predominantly of mild severity, have been reported in 6.5% to 31% of patients in phase II trials in breast, non-small cell and ovarian carcinomas (Canobibo *et al.*, 1989; Fumoleau *et al.*, 1990; Depierre *et al.*, 1991; George *et al.*, 1989). Severe peripheral neuropathy and paralytic ileus have occurred infrequently and have been reversible following discontinuation of therapy (Besenval *et al.*, 1989). Muscle weakness has also been noted in patients treated for 3 to 6 months; however, these effects have also been reversible after discontinuation of

NVB. Tumor pain and jaw pain have also been noted.

2.7.5.3. Gastrointestinal.

The most common gastro-intestinal effect of NVB has been constipation (see Section 2.7.5.2, Neurologic toxicities). Although nausea and vomiting has been reported in up to 20% of patients (Depierre et al., 1991), WHO grade 3 to 4 toxicity has been experienced by only 2.6% to 8.1% of patients in phase II trials (Canobibo et al., 1989; Fumoleau et al., 1990; George et al., 1989; Depierre et al., 1991). Mild stomatitis has also been reported (Canobibo et al., 1989).

2.7.5.4. Local reactions.

Phlebitis, characterized by erythema and tenderness extending along the palpable length of the infused vein, has occurred with NVB. Severe venous pain and/or thrombophlebitis, occasionally requiring the use of central venous catheters for subsequent administration of the agent, have been reported in 5.4% to 30% of patients in phase II studies (Canobibo et al., 1989; George et al., 1989; Tresca et al., 1990; Depierre et al., 1991). The severity of extravasation reactions observed to date would also indicate that NVB is a moderate vesicant. Mild to moderate alopecia has been fairly common and appears to be related to the duration of treatment; complete, but reversible hair loss, has been reported in 8.0% to 11% of patients (Canobibo et al., 1989; George et al., 1989; Depierre et al., 1991).

2.7.5.5. Miscellaneous.

Chest pain that is occasionally associated with EKG changes suggestive of ischemia, has been noted in less than 1% of patients receiving NVB. One 61-year-old man who had several episodes of chest pain following NVB treatment, had a myocardial infarction and expired five days after his second treatment. However, the overwhelming majority of these complaints have occurred in patients with intrathoracic malignancies and it has not been possible to determine whether the chest pain represents a drug-related phenomenon, a manifestation of tumor pain or exacerbation of underlying atherosclerotic cardiovascular disease. Reversible dyspnea has also been observed following treatment. In addition, transient elevations in liver function tests have been noted.

3. TAXANES

The taxanes are a unique class of structurally complex natural and semi-synthetic products which possess cytotoxicity by virtue of their unique antimicrotubule effects. The chemistry of these agents, especially the protypic taxane, has been comprehensively reviewed (Kingston et al., 1990).

3.1. TAXOL

The antimicrotubule agent taxol (Fig. 3), the first compound with a taxane ring demonstrated to possess antineoplastic activity, has become one of the most important lead compounds to recently emerge from the screening of natural products as anticancer agents. Interest in taxol dates from the late 1960s when a crude extract of bark from the Pacific yew Taxus brevifolia was tested by the National Cancer Institute (NCI) in a large scale screening program and was found to possess cytotoxic activity against several murine tumors. Taxol was later identified as the active constituent of the extract in 1971 by Wall and co-workers (Wani et al., 1971). Despite promising antitumor properties, its development progressed slowly due to its scarcity and the difficulty in isolating and extracting the agent. In addition, the poor aqueous solubility of taxol hampered the development of a suitable clinical formulation. Interest in taxol was later rekindled by the discovery of its unique cytotoxic mechanism as a promoter of microtubule assembly (Schiff et al., 1979; Schiff and Horwitz, 1980). At the present time, taxol is undergoing a broad evaluation in investigational studies to determine the spectrum of its clinical antitumor activity. Its preclinical and clinical properties have recently been reviewed (Rowinsky et al., 1990).

3.1.1. Mechanisms of Action

Taxol's mechanism of action was elucidated by Horwitz and co-workers in 1979 (Schiff et al., 1979; Schiff and Horwitz, 1980, 1981; Parness and Horwitz, 1981; Manfredi et al., 1982; Parness et al., 1983; Manfredi and Horwitz, 1984b). These investigators demonstrated that taxol binds preferentially to microtubules rather than tubulin dimers with a stoichiometry approaching one mole of taxol per mole of polymerized tubulin dimer (Parness and Horwitz, 1981). The binding of taxol to polymerized tubulin is reversible, and the binding constant is approximately $0.9 \, \mu\text{mol/l}$ (Parness and Horwitz, 1981; Collins and Vallee, 1987). The binding site for taxol is different from the binding sites for exchangeable GTP, colchicine, VBL, and podophyllotoxin (Kumar, 1981;
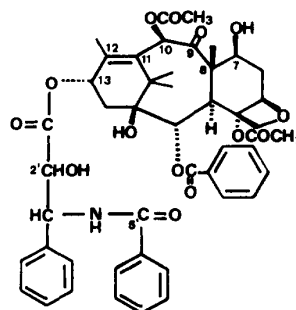

FIG. 3. Structure of taxol.

Schiff and Horwitz, 1981). Unlike other antimicrotubule agents such as the vinca alkaloids and colchicine that induce microtubule disassembly, taxol stabilizes microtubules and shifts the dynamic equilibrium towards microtubule assembly (Schiff et al., 1979; Schiff and Horwitz, 1980, 1981; Kumar, 1981; Parness and Horwitz, 1981; Manfredi et al., 1982; Carlier and Pantaloni, 1983; Fujii et al., 1983; Parness et al., 1983; Manfredi and Horwitz, 1984b; Salmon et al., 1984; Wilson et al., 1985; Wallin et al., 1986; Collins and Vallee, 1987). Taxol concentrations as low as 0.05 μM promote microtubule assembly and decrease the lag time for microtubule assembly in vitro (Schiff et al., 1979). Taxol is even active in the absence of factors that are usually essential for microtubule assembly, such as exogenous GTP or microtubule-associated proteins (MAPs) (Hamel et al., 1981; Schiff and Horwitz, 1981). Taxol-treated microtubules are stable even after treatment with calcium or low temperatures, conditions that usually promote disassembly (Schiff et al., 1979; Schiff and Horwitz, 1980; Thompson et al., 1981). This unusual stability results in the inhibition of the essential dynamic processes of the microtubule network.

Studies with HeLa cells and BALB/c fibroblasts treated with low taxol concentrations (0.25 μM) that produce minimal inhibition of DNA, RNA, and protein synthesis (Schiff et al., 1979), and studies of murine P388 leukemia, have demonstrated that taxol blocks cell cycle traverse in mitosis (Fuchs and Johnson, 1978; Schiff et al., 1979; Schiff and Horwitz, 1980). Taxol has also been demonstrated to affect cells in non-mitotic cell cycle phases such as the prevention of G_0 to S phase transition in fibroblasts during stimulation of DNA synthesis by growth factors and delay of traverse of sensitive leukemia cells in non-mitotic phases of the cell cycle (Crossin and Carney, 1981; Rowinsky et al., 1988). In addition, taxol has been shown to inhibit shape changes and locomotion in Walker 256 carcinosarcoma cells (Keller and Zimmerman, 1986) and inhibit steroidogenesis in human Y-1 adrenocortical and MLTC-1 Leydig tumors by decreasing the intracellular transport of cholesterol side-chain cleavage enzymes (Rainey et al., 1985). These effects on locomotion, shape and transport appear to be related to perturbations in microtubule dynamics.

Taxol also inhibits specific functions in many non-malignant cells such as chemotaxis, migration, cell spreading, polarization, generation of hydrogen peroxide, and killing of phagocytized microorganisms in human polymorphonuclear leukocytes (Roberts et al., 1982; Iannone et al., 1987). In addition, taxol antagonizes the effects of microtubule disrupting drugs on lymphocyte function and cAMP metabolism, and inhibits the proliferation of stimulated human lymphocytes (Cuthbert and Shay, 1983; Wolberg et al., 1984). Taxol also mimics the effects of endotoxic bacterial lipopolysaccharide on macrophages resulting in a rapid decrement of tumor

necrosis factor-alpha (TNF-alpha) receptors and TNF-alpha release (Ding et al., 1990). In an in vitro model of proliferative vitreoretinopathy which may be relevant to the treatment of traction retinal detachment and proliferative vitreoretinopathy, taxol has been shown to inhibit chorioretinal fibroblast proliferation and contractility (van Bochxmeer et al., 1985). Finally, taxol has been demonstrated to inhibit the secretory functions of many specialized cells such as insulin secretion in isolated rat islets of Langerhans (Howell et al., 1982), protein secretion in rat hepatocytes (Oda and Kehara, 1982; Kaufman et al., 1986), and the nicotinic receptor-stimulated release of catecholamines from chromaffin cells of the adrenal medulla (Thuret-Carnahan et al., 1985; McKay, 1989).

Micromolar concentrations of taxol have also been demonstrated to induce unique morphologic changes and block the replication of Trypanosoma cruzi, the causative agent of South American trypanosomiasis, for which there is no curative therapy (Baum et al., 1981). Therefore, taxol may have potential as an antiprotozoal agent, as well.

3.1.2. Preclinical Antineoplastic Activity

Taxol was reported to be moderately active against murine L1210, P388, and P1534 leukemias, and the Walker 256 carcinosarcoma, Sarcoma 180 and Lewis lung tumor, and cytotoxic in the KB cell culture system in early studies (Wani et al., 1971); however, it was not selected for development by the NCI until 1977. At that time, the decision to develop taxol was based on the discovery of its unique mechanism of cytotoxic action and impressive activity against the murine B16 melanoma model (National Cancer Institute, 1983). Taxol also demonstrated good antitumor activity against several human tumor xenografts in the NCI's tumor screening panel of the late 1970s including the MX-1 mammary tumor implanted beneath the renal capsule of athymic mice when administered subcutaneously, and moderate activity against similar xenografts of human CX-1 colon and LX-1 lung tumors (National Cancer Institute, 1983). Moderate activity against intraperitoneal-implanted P388 and L1210 murine leukemias was also confirmed, but it was ineffective against the murine subcutaneous-implanted $CD8F_1$ mammary and colon 38 carcinomas and intravenous implants of Lewis lung carcinoma. Investigations of schedule dependency in the P388 leukemia system revealed that increased lifespan was maximal when mice were treated every 3 hr, which approximates a continuous administration schedule.

Taxol also demonstrated good cytotoxic activity against several human tumors in early studies performed by a number of investigators including significant activity in human breast, endometrial, ovarian, brain, tongue, and lung tumor xenografts in athymic mice (Jacrot et al., 1983; Riondel et al., 1986, 1988)

and the human prostatic carcinoma cell line LNCaP
with concentrations as low as 10 nmol/l for 9 days
(Roytta et al., 1987). In studies that focused on
developing more efficient screening systems for new
antineoplastic agents, Fan et al. (1987) compared
the anti-tumor activities of several standard and
investigational antitumor agents at equivalent
granulocyte-macrophage colony-forming cell (GM-
CFC) inhibitory concentrations in a primary human
tumor cell culture assay. Active standard agents that
were tested at concentrations up to their IC_{90} for
GM-CFC produced $\geqslant 50\%$ inhibition of growth in
at least 30% of human tumors. Responses with
the investigational agents taxol, caracemide, and
spirogermanium were 78%, 9% and 7%, respectively
(Fan et al., 1987). Based upon this model and knowl-
edge that myelosuppression was emerging as taxol's
principal clinical toxicity in concurrent phase I stud-
ies, these investigations predicted that taxol would be
a clinically efficacious antineoplastic agent.

3.1.3. Mechanisms of Resistance

Two potential mechanisms of acquired resistance
to taxol have been characterized. First, some Chinese
hamster ovary (CHO) cell lines with acquired taxol
resistance possess altered alpha- or beta-tubulin and
require taxol in their medium for normal growth
(Cabral, 1983; Cabral et al., 1983, 1986). These
resistant cells lack normal microtubules in their inter-
polar mitotic spindles when grown in the absence of
taxol resulting in impaired microtubule assembly.
Continuous exposure to taxol is required for polym-
erization to occur normally, thereby promoting the
formation of functional microtubules. A second well-
documented mechanism of acquired taxol resistance
involves the multi-drug resistant (mdr) phenotype
similar to that described previously for the vinca
alkaloids (Gupta, 1983, 1985; Roy and Horwitz,
1985; Horwitz et al., 1986; Racker et al., 1986; Brewer
and Warr, 1987; Moscow and Cowan, 1988). A
phosphoglycoprotein $(M_r$ 135,000) has also been
identified which accounts for 4% to 5% of the total
membrane protein of a murine macrophage cell line
(J774.2) that is 800-fold more resistant to taxol
compared to its parental line (Roy and Horwitz,
1985; Horwitz et al., 1986). In the continuous pres-
ence of taxol, these cells accumulate less drug at
steady-state than taxol-sensitive parental cells. They
are also cross-resistant to colchicine, VBL, actino-
mycin D, and doxorubicin, but sensitive to
bleomycin. However, these cells become progressively
more sensitive to taxol and develop progressively
lower levels of the M_r 135,000 membrane glyco-
protein as durations in drug-free medium are pro-
longed. Additionally, two groups of low-level
VCR-resistant CHO lines have been characterized
which may shed light on mechanisms of acquired
taxol resistance including: (a) cell lines that were
cross-resistant to taxol and felt to be membrane

mutants due to their decreased ability to accumulate
VCR and reversal of resistance with calcium channel
blockers; and (b) cell lines that were sensitive to taxol
and felt to be tubulin mutants (Brewer and Warr,
1987).

Although the precise mechanisms that account for
inherent resistance to taxol have not been clearly
defined, the sensitivity of several human leukemia cell
lines to taxol was directly related to the taxol-induced
formation of irreversible microtubule bundles
(Rowinsky et al., 1988; Roberts et al., 1989, 1990).
Whereas sensitive cell lines primarily formed irrevers-
ible bundles and were critically affected during inter-
phase, most relatively-resistant cells were unaffected
during traverse through G_0/G_1 and S phases and
accumulated in G_2/M with multiple abnormal asters
(Rowinsky et al., 1988). Most resistant cells that
formed asters also contained polyploid DNA content
after prolonged drug exposure. The magnitude of
polyploidization appeared to be related to resistance
(Roberts et al., 1990). Interestingly, in a phase I trial
of taxol in leukemia, the sensitivity of leukemic blasts
to form microtubule bundles was directly related to
the magnitude of clinical antitumor activity (Rowin-
sky et al., 1989). These studies suggest that morpho-
logic microtubule effects and the state of DNA
polyploidization may be useful indices of drug sensi-
tivity which could be performed on clinical material
and evaluated prospectively in clinical trials.

3.1.4. Clinical Pharmacology

Taxol's aqueous insolubility hampered the devel-
opment of a suitable analytical assay which resulted
in a lack of detailed pharmacologic information when
the agent entered into clinical trials. Although several
assays had previously been developed (Hamel et al.,
1982; Mellado et al., 1984), they were tedious and not
generally applicable to clinical trials. For example,
Hamel et al. (1982) described a unique biochemical
assay with a sensitivity of 0.1 μM. This assay exploited
taxol's ability to induce tubulin to form cold-resistant
polymers that hydrolyze GTP at 0°C. Hamel et al.
(1982) found that taxol was almost entirely bound to
plasma proteins (92%) and rapidly cleared from
serum of rabbits. The alpha and beta $t_{\frac{1}{2}}$s of taxol
administered as an i.v. bolus to a single rabbit were
2.7 and 45 min, respectively (Hamel et al., 1982).

Highly sensitive and specific reverse-phase HPLC
assays capable of measuring taxol concentrations as
low as 50 nmol/l were developed during early clinical
trials (Longnecker et al., 1986; Grem et al., 1987;
Wiernik et al., 1987a,b; Rowinsky et al., 1989; Brown
et al., 1991). Taxol's pertinent pharmacokinetic par-
ameters are summarized in Table 1. The agents
plasma elimination has been described as biexponen-
tial. Although there has been wide interpatient vari-
ability in alpha and beta $t_{\frac{1}{2}}$s, there has not been any
evidence for nonlinearity nor dose dependency.
Alpha and beta $t_{\frac{1}{2}}$s have ranged from 0.27 to 0.32 hr

TABLE 1. *Taxol Pharmacokinetic Parameters*

Schedule	Model	$t_{\frac{1}{2}}$ (hr) a	b	Cl (ml/min/m^2)	C_p (μM) (Dose)	VD_{ss} (l/m^2)	MRT (hr)	Urine (% dose)
6 hr infusion (Wiernik et al., 1987b)	Biphasic	0.32	8.6	100	3.2–8.1 (175–275 mg/m^2)	55	8.6	5.2
24 hr infusion (Wiernik et al., 1987a)	Biphasic	0.27	3.9	993	0.6–0.94 (200–275 mg/m^2)	182	19.9	1.4
1–6 hr infusion q d × 5d (Grem et al., 1987)	Biphasic	—	1.3	833	0.06–0.37 (15–40 mg/m^2)	81	—	6.6
1–6 hr infusion (Donehower et al., 1987)	Biphasic	0.27	6.4	253	1.3–13.0 (60–265 mg/m^2)	67	5.6	5.9
24 hr infusion (Rowinsky et al., 1989)	—	—	—	—	1.6–3.5 (250–390 mg/m^2)	—	—	—
6 hr infusion (Brown et al. 1991)	Biphasic	—	4.8	300	2.3–4.6 (175–275 mg/m^2)	167	11.8	—
Mean	—	0.29	5.0	496	—	110	11.5	4.8
(SD)		(0.03)	(2.7)	(392)		(59)	(6.2)	(2.3)

$t_{\frac{1}{2}}$a alpha half-title; $t_{\frac{1}{2}}$b beta half-life; C_p peak plasma concentration; Cl systemic clearance; VD_{ss} volume of distribution at steady-state; MRT mean resonance time.

(mean, 0.29 hr) and 1.3 to 8.6 hr (mean, 5.0 hr), respectively. Despite extensive binding to plasma proteins (95–98%), taxol is readily eliminated from plasma which is consistent with limited preclinical data. Steady-state volume of distribution have been quite large; mean values have ranged from 55 to 183 l/m^2 (mean, 110 l/m^2).

Systemic clearances for taxol have ranged from 100 to 993 ml/min/m^2 (mean, 496 ml/min/m^2) (Longnecker et al., 1986; Grem et al., 1987; Wiernik et al., 1987a,b; Rowinsky et al., 1989; Brown et al., 1991), but the principal mechanisms of systemic clearance are not entirely known. Total urinary excretion has been insignificant (range 1.4–6.6%; mean 4.8%), which indicates that renal clearance contributes minimally to systemic clearance. This suggests that metabolism, biliary excretion, and/or extensive tissue binding are responsible for the bulk of systemic clearance. In fact, high taxol concentrations and unidentified metabolites have recently been measured in the bile of two patients with biliary catheters (E. K. Rowinsky, unpublished data). Metabolites in human blood and urine have not been identified, but minor (<5%) spontaneous conversion of taxol to 7-epitaxol has been demonstrated in normal saline solutions at 37°C after 48 hr, and in tissue culture (Ringel and Horwitz, 1987; Brown et al., 1991). Moreover, it has been determined that the liver plays a significant role in metabolizing taxol in rats (Monsarrat et al., 1990). These investigators have demonstrated that 11.5% and 29% of injected taxol is recovered in rat bile as taxol and metabolites, respectively. Two major metabolites are hydroxylated. Interestingly, these metabolites are as active as taxol in preventing microtubule disassembly; however, they are also 9- and 39-fold less cytotoxic than taxol against L1210 leukemia in vitro.

To date, taxol has been measured in the ascites of one patient 7 hr post-infusion and maintained for at least 12 hr at concentrations that were 40% of concurrent plasma levels (Wiernik et al., 1987b). How-

ever, taxol was not detected post-infusion in the cerebrospinal fluid of leukemia patients (Rowinsky et al., 1989). More importantly, the range of peak plasma taxol concentrations achieved on all schedules have been demonstrated to be capable of inducing significant biologic and cytotoxic effects in clinical specimens in vitro (Rowinsky et al., 1988).

3.1.5. Dose and Schedule

Although taxol has been administered on various schedules in phase I trials (see Section 3.1.6., Clinical Trials), the frequency and severity of acute hypersensitivity reactions (HSRs) have apparently been more common with shorter infusion schedules (see Section 3.1.8.2, Hypersensitivity Reactions). Therefore, the NCI has recommended that all phase II taxol trials utilize a 24 hr continuous infusion schedule with a prophylactic anti-allergic premedication regimen such as the following: (a) dexamethasone 20 mg orally or intravenously 14 and 7 hr before treatment; (b) diphenhydramine 50 mg intravenously 30 min before treatment; and (c) an H$_2$-histamine antagonist such as cimetidine (300 mg), ranitidine (50 mg), or famotidine (20 mgs) intravenously 30 min before treatment. Taxol doses of 200 to 250 mg/m^2 over 24 hr have been recommended for untreated or minimally pretreated patients, respectively, while taxol doses of 110 to 170 mg/m^2 have been well tolerated in more heavily-pretreated patients (see Section 3.1.6, Clinical Trials).

3.1.6. Clinical Trials

3.1.6.1. *Phase I.* Phase I trials of taxol administered on several schedules were begun in 1983 under the auspices of the NCI, but a high incidence HSRs led to the discontinuation of many studies and threatened the prospects for taxol's further development. Table 2 lists all completed phase I studies, principal toxicities, and recommended phase II and maximum

TABLE 2. *Phase I Studies of Taxol*

Institution[c]	Schedule	MTD[a] (PII)	DLT[b]	Other principal effects
JHOC[c] (Donehower *et al.*, 1987)	1–6 hr infusion q 21 day	265 mg/m² (210)	Neutropenia	Neuropathy, Mucositis, Arthralgias/Myalgias, HSRs[d]
Einstein[c] (Wiernik *et al.*, 1987b)	1–6 hr infusion q 21 day	275 mg/m² (250)	Neutropenia Neuropathy	HSRs, Alopecia, Mucositis
Einstein (Wiernik *et al.*, 1987a)	24 hr infusion q 21 day	275 mg/m² (250)	Neutropenia Neuropathy	HSRs
Memorial (Kris *et al.*, 1986)	3 hr infusion q 21 day	190 mg/m² (—)	HSRs	Leukopenia, Nausea, Alopecia
UTSA (Brown *et al.*, 1991)	6 hr infusion q 21 day	275 mg/m² (225)	Neutropenia	Arthralgias/Myalgias, Mucositis, Alopecia HSRs, Neuropathy
Mt Sinai (Ohnuma *et al.*, 1985b)	24 hr infusion q 21 day	200 mg/m² (—)	Neutropenia	Alopecia, Nausea, Vomiting
MDA (Legha *et al.*, 1986)	1 hr infusion daily × 5 q 21 day	40 mg/m² (20)	Neutropenia	Alopecia, Diarrhea,
Wisconsin (Grem *et al.*, 1967)	1–6 hr infusion daily × 5 q 21 day	40 mg/m² (30)	Neutropenia	HSRs, Nausea, Vomiting, Alopecia, Mucositis, Thrombocytopenia
JHOC (leukemia) (Rowinsky *et al.*, 1989)	24 hr infusion q 14–21 day	390 mg/m² (310)	Mucositis	Neutropenia, HSR Neuropathy
JHOC (Rowinsky *et al.*, 1991a)	24 hr infusion +Cisplatin	135–170 +75 mg/m² q 21 d	Neutropenia	Arthralgias/Myalgias Alopecia, Cardiac, HSR, Neuropathy

[a]Maximum tolerated dose (recommended phase II dose).
[b]Dose limiting toxicity.
[c]Infusion duration lengthened during study due to HSRs and premedications added (steroids, H_1 and H_2 antihistamines). Listed *MTD* (PII) and *DLT* reflect longest duration of infusion with premedications.
[d]Hypersensitivity reactions.
[e]JHOC, John Hopkins Oncology Center; MDA, MD Anderson; UTSA, University of Texas at San Antonia.

tolerated doses (MTD). Neutropenia was the major dose-limiting toxicity in all phase I solid tumor trials (Ohnuma *et al.*, 1985b; Legha *et al.*, 1986; Grem *et al.*, 1987; Donehower *et al.*, 1987; Wiernik *et al.*, 1987a,b; Brown *et al.*, 1991) with the exception of one 3-hr infusion study in which frequent HSRs precluded further dose escalation (Kris *et al.*, 1986). Some investigators also found that both peripheral neurotoxicity and neutropenia were dose-limiting toxicities with 6 and 24 hr infusions (Wiernik *et al.*, 1987a,b). However, neurotoxicity was not particularly prominent at comparable taxol doses in other phase I/II studies. In fact, mucositis was the non-hematological dose-limiting toxicity of taxol in leukemia patients who were treated with higher doses than those that induced severe neutropenia in solid tumor patients (Rowinsky *et al.*, 1989). Although it was anticipated that neurotoxicity might preclude treatment with combinations of taxol and other neurotoxic agents like cisplatin, subjective and objective evidence of neurological dysfunction were insignificant in a phase I combination study of taxol and cisplatin (Rowinsky *et al.*, 1991a). Instead, neutropenia was the principal dose-limiting toxicity of this drug combination. Based on data indicating that taxol and cisplatin induce maximal cytotoxicity of L1210 leukemia when treatment with taxol precedes cisplatin (Citardi *et al.*, 1990), this study also evaluated the relative toxicities and MTDs of alternate sequences of drug treatment and demonstrated that

neutropenia was more severe when cisplatin preceded taxol compared to the alternate sequence (Rowinsky *et al.*, 1991a). This phenomenon may be explained by a 25% reduction in the clearance of taxol when cisplatin precedes taxol (Rowinsky *et al.*, 1991a).

Antineoplastic activity has been observed in several tumor types during early phase I trials including melanoma, adenocarcinoma of unknown origin, advanced and cisplatin-refractory ovarian, non-small cell lung, gastric, colon, and head and neck carcinomas, ALL and ANLL (Ohnuma *et al.*, 1985b; Kris *et al.*, 1986; Legha *et al.*, 1986; Grem *et al.*, 1987; Donehower *et al.*, 1987; Wiernik *et al.*, 1987a,b; Rowinsky *et al.*, 1989). To date, the combination of taxol and cisplatin with and without granulocyte colony-stimulating factor have also induced a pathologically documented complete response in a patient with an advanced large cell lung carcinoma, and antineoplastic activity has been noted in other patients with advanced non-small cell lung, breast, head and neck, colon, pancreatic and advanced ovarian carcinomas, and melanoma (Rowinsky *et al.*, 1991a; E. K. Rowinsky, unpublished).

Abdominal pain has been the dose-limiting toxicity of taxol administered to patients with ascites, particularly due to ovarian carcinoma, with the intra-cavitary maximum tolerated dose ranging from 170 to 200 mg/m² every 3 weeks (Markman *et al.*, 1991; E. K. Rowinsky, unpublished). Adverse systemic effects, including alopecia and sporadic neutropenia, were

also observed and low concentrations of taxol have been measured in blood. However, intracavitary/systemic taxol concentration ratios have exceeded 150- to 800-fold, with an even greater AUC advantage (Markman *et al.*, 1991). These pharmacologic characteristics indicate that taxol may be an optimal agent to administer by the intraperitoneal route.

3.1.6.2. First generation phase II trials. Initially, shortages in taxol's supply precluded the initiation of conventional broad phase II trials. Instead, limited phase II trials have been performed in specific neoplasms based on anti-tumor activity observed in preclinical and early phase I studies. The first generation of phase II studies that used 24 hr administration schedules and prophylactic premedications have been completed in melanoma, renal cell and advanced ovarian carcinomas. In renal cell carcinomas, taxol appeared to have a low level of activity in that no responses were observed in 18 patients treated with 250 mg/m^2 (Einzig *et al.*, 1988). Taxol has been noted to have some activity in melanoma. It was active in preclinical murine models and some responses were observed in phase I trials (Wiernik *et al.*, 1987a,b). However, disparate responses of 6% and 18% have been noted in 2 phase II trials completed to date (Legha *et al.*, 1990; Einzig *et al.*, 1991).

3.1.6.3. Ovary. To date, taxol's most exciting antineoplastic activity has clearly been in advanced ovarian epithelial neoplasms. McGuire *et al.* observed 11 partial, 1 pathologically documented complete, and 7 minor responses of relatively long durations in 40 evaluable patients (McGuire, W. P. *et al.*, 1989). Besides demonstrating an extraordinarily high response rate in patients with advanced disease, these results have been particularly important for two other reasons. First, most patients including responders were heavily-pretreated with radiation and chemotherapy (mean number of prior chemotherapy regimens per patients—2.7) and most patients were refractory to cisplatin. Second, the doses of taxol given to most patients were significantly lower due to limited hematopoietic tolerance than doses that were previously demonstrated to be safe in minimally pretreated or untreated patients (200 to 250 mg/m^2). The Gynecology Oncology Group (GOG) and investigators at Albert Einstein Medical Center have completed confirmatory studies in advanced ovarian cancer and have verified that taxol possesses activity in advanced and refractory ovarian cancer (Thigpen *et al.*, 1990; Einzig *et al.*, 1989). The Gynecology Oncology Group reported an overall response rate of 37% including responses in 7 of 14 (50%) patients who could not be considered resistant to cisplatin (progression >6 months after cisplatin) and 8 of 24 patients (33%) with cisplatin resistance (progression on or <6 months after cisplatin) (Thigpen *et al.*, 1990).

3.1.6.4. Second generation phase II trials. Excitement generated by phase II trials of taxol in advanced and refractory ovarian carcinoma and the diverse activity reported with taxol in phase I trials was the impetus for obtaining adequate supplies of taxol to launch broad phase II trials in 1990–1991. These include phase II trials in breast, non-small cell and small cell lung, colon, prostate, cervical and head and neck carcinomas. Preliminary results in previously treated (1 prior regimen) patients with breast carcinoma have also been very exciting (Holmes *et al.*, 1991a, b). Initially, patients received 250 or 200 mg/m^2 of taxol if they had previously been treated with radiotherapy. Complete and partial responses have occurred in 12% and 44% of patients, respectively. The median response duration was greater than 5 months. Neutropenia was profound at these starting doses and most patients required dose reductions during subsequent courses. However, neutropenia with fever occurred in only 5% of courses.

3.1.7. Future Directions

Responses in advanced and cisplatin-refractory ovarian carcinomas have generated considerable enthusiasm for the further development of taxol. These results have been reminiscent of early studies with cisplatin in the 1970s, in which response rates of approximately 30% occurred in drug-refractory ovarian cancer and 50% to 60% in untreated patients (Wiltshaw *et al.*, 1979, 1988). Defining the role of taxol in first and second line treatment for untreated as well as refractory and recurrent disease patients with ovarian cancer has become a goal in the development of this agent. To partially accomplish this goal, a phase III study of taxol and cisplatin versus cisplatin and cyclophosphamide is currently accruing patients with suboptimal stage 3 and stage 4 ovarian carcinoma. In addition to pivotal trials in ovarian cancer, the current development program is directed towards evaluating the spectrum of taxol's activity in other disease sites. Several phase II trials (breast, non-small and small cell lung, gastric, colon prostate, head and neck, and cervical carcinomas) have recently opened to patient accrual. With the exciting activity observed with taxol in patients with advanced breast cancer (Holmes *et al.*, 1991), subsequent phase II combination studies of taxol and doxorubicin with and without hematopoietic colony-stimulating factors in advanced breast carcinoma are ongoing (Rowinsky and Donehower, 1991). In addition, phase I and II testing is being planned in the pediatric population. The question of dose intensification in solid tumors will be also addressed in phase I trials of colony-stimulating factors and taxol (single agent and in combination with cisplatin).

Encouraging results in ongoing and subsequent phase II and III studies will be to no avail without a feasible long-term solution to the problem of supplying adequate quantities of taxol or identifying

suitable analogs for widespread clinical use (Borman, 1991). One possible option may be the hemisynthesis of taxol or active analogs from more abundant natural compounds such as baccatin III, a less complex diterpenoid that is derived from the needles of *Taxus baccata*. Both taxol and an active related compound taxotere (RP 56976) have already been synthesized from baccatin III. Another avenue of exploration is the extraction of precursors of taxol and analogs such as taxotere from yew needles harvested from yew bushes (Denis and Greene, 1988). Bushes would remain intact and may serve as a renewable source of yew needles. Improvements in plant cell culture techniques have also permitted investigators to grow taxol-producing plant cells *in vitro* which may potentially provide a viable solution to the current supply problem (Christian *et al.*, 1989).

3.1.8. Toxicities

3.1.8.1. Hematologic.
Neutropenia, the principal dose-limiting toxicity of taxol, has not been schedule-dependent (Ohnuma *et al.*, 1985b; Kris *et al.*, 1986; Legha *et al.*, 1986, 1990; Grem *et al.*, 1987; Donehower *et al.*, 1987; Wiernik *et al.*, 1987a,b; Einzig *et al.*, 1988, 1989, 1991; McGuire, W. P. *et al.*, 1989, 1990). The onset of neutropenia is usually by day 8, and nadir neutrophil counts generally occur on days 8 to 11 with rapid recovery by days 15 to 21. Febrile and/or septic episodes associated with severe neutropenia are infrequent, which is probably due to the short duration of neutropenia. In fact, 213 of 281 courses given to heavily pretreated ovarian cancer patients were associated with nadir absolute neutrophil counts (ANCs) <1000 cells/μl. Nadir ANCs generally remained unchanged during successive courses indicating that taxol may not be irreversibly toxic to hematopoietic stem cells. The major clinical risk factor for neutropenia appears to be the extent of prior myelotoxic chemotherapy and/or radiation. Longnecker *et al.* (1986) demonstrated that AUCs correlated with white blood cell count nadirs, changes in the absolute white blood cell count, and percent decreases in the absolute white blood cell count. Significant anemia and thrombocytopenia have rarely been observed, even in heavily-pretreated patients, and even in the presence of severe neutropenia.

3.1.8.2. Hypersensitivity reactions.
A major concern during early clinical studies of taxol was the occurrence of HSRs. The characteristics of 32 patients who had HSRs from 1983 to 1988 have been reviewed by Weiss *et al.* (1990). They reported on 27 patients who had definite manifestations of Type I HSRs which suggested that the HSRs were most likely mediated by the release of histamine. These 27 patients had at least two of the following signs and symptoms: hypotension, dyspnea with bronchospasm, and urti-

caria. Five other patients also experienced manifestations suggesting HSRs such as generalized erythema, hypotension alone, pruritis without skin lesions, or dyspnea without bronchospasm. Fifty-three percent of definite HSRs occurred within 2 to 3 min of beginning taxol with some patients receiving only 2 to 3 mg of drug, and 78% had symptoms within 10 min of starting taxol. The other reactions began 30 to 90 min after starting, but two patients developed HSRs 3 and 12 hr after completing taxol. One fatal reaction that was characterized by the rapid development of hypotension and asystole occurred, but all other patients recovered fully without any adverse consequences after various treatments including administration of fluids, antihistamines, vasopressors, corticosteroids, and aminophylline. Seven patients, including 5 patients who received prophylactic anti-allergic drugs, received subsequent courses of taxol without further problems.

Due to taxol's aqueous insolubility, it is formulated in 50% dehydrated alcohol, USP, and 50% polyoxyethylated castor oil (Cremophor EL) which is known to induce HSRs in both dogs and humans (Lorenz *et al.*, 1977; Lassus *et al.*, 1985). Taxol-induced HSRs do not seem to be due to IgE directed against taxol or its Cremophor vehicle since most episodes have occurred during first treatment, and prior sensitization to an antigen is generally felt to be necessary for the development of an IgE response. Weiss *et al.* reported that HRSs occurred with the first dose of taxol in 18 patients, the second dose in 13 patients, and the sixth dose in 1 patient (Weiss *et al.*, 1990). It seems more plausible that these HSRs are nonimmunologically mediated by the direct release of histamine or other vasoactive substances from mast cells and basophils. This is analogous to the presumed mechanism for HSRs due to iodinated radiocontrast dyes (Brasch *et al.*, 1970; Lesser *et al.*, 1971). It is also unclear whether taxol itself or its Cremophor vehicle is principally responsible for HSRs. Other drugs formulated in Cremophor such as cyclosporin A, teniposide, vitamin K, and didemnin B have been associated with similar HSRs, but the clinical formulation of therapeutic taxol doses requires the greatest amount of Cremophor relative to these other agents (Lassus *et al.*, 1985).

Initially, HSRs appeared to be indirectly related to the duration of the taxol infusion, and therefore to the concentration of taxol and Cremophor in the infusate. However, HSRs have been observed with the longer 24 hr infusions as well. In fact, Weiss *et al.* (1990) reported that HSR incidence were 16%, 13%, and 7% with 3, 6, and 24 hr infusions, respectively, and that the majority of patients who has HSRs received taxol over 24 hr after receiving prophylactic premedications. After HSRs were recognized as a significant problem, the consensus of the NCI and investigators evaluating taxol was that subsequent phase I/II studies should utilize 24 hr infusions and prophylactic anti-allergic premedications including

dexamethasone, the H_1-histamine antagonist diphen-hydramine, and an H_2-histamine antagonist such as cimetidine or ranitidine (see Section 3.1.5, Dose and Schedule). This recommendation was, in part, based on the successful prophylaxis of HSRs by similar regimens in patients who were allergic to iodinated radiocontrast agents (Schatz et al., 1975; Shedadi, 1975; Karliner et al., 1981). Initially, these premedications appeared to reduce the incidence and severity of HSRs. However, it was later recognized that they were not fully protective (Donehower et al., 1987; Wiernik et al., 1987b). In fact, 11 of the 27 definite Type I HSRs in the series of Weiss et al. (1990) occurred despite these prophylactic measures and other episodes associated with 24 hr infusions and prophylactic premedications have been reported since Weiss' original series (McGuire, W. P. et al., 1989; Thigpen et al., 1990; Einzig et al., 1991; Rowinsky et al., 1991a). At the Johns Hopkins Oncology Center, however, only 1 HSR occurred in each of 3 subsequent trials involving 24 hr infusions and prophylactic premedications. These trials involved 108 patients who received 522 courses of taxol (Rowinsky et al., 1989, 1991a; McGuire, W. P. et al., 1989). Although the true incidence of HSRs and the relative benefits of specific administration schedules and premedication regimens are not clearly known, the NCI has recommended that subsequent studies of taxol utilize 24 hr infusions and prophylactic anti-allergic premedications.

3.1.8.3. *Gastrointestinal toxicity.* Mucositis was rarely observed in phase I studies in solid tumors (Donehower et al., 1987) but it was the major non-hematologic dose-limiting toxicity in a phase I study evaluating high taxol doses in leukemia patients and precluded dose escalation above 390 mg/m^2 (Rowinsky et al., 1989). At the recommended phase II dose for leukemia patients, 315 mg/m^2, severe mucositis occurred only during second or subsequent courses which suggested that this toxicity was, in part, cumulative. Taxol-induced mucositis is characterized by diffuse ulcerations of the lips, oral cavity, and pharynx. Dysphagia and pain reflecting esophageal involvement are also common. Postmortem examinations have revealed mucosal ulcerations in the oropharynx, esophagus, and intestines without evidence of viral, fungal, or bacterial mucosal invasion. Ultrastructurally, an accumulation of epidermal cells with taxol-induced asters has been evident in ulcerated mucosa indicating cell cycle arrest in mitosis (Hruban et al., 1989). Taxol-related gastrointestinal toxicities have also included nausea, vomiting and diarrhea which have generally been infrequent and modest in severity.

3.1.8.4. *Neurological.* Taxol has been demonstrated to inhibit neurite growth and induce prominent morphologic effects such as microtubule bundles in neurons, satellite cells, and Schwann cells in organo-typic dorsal root ganglion-spinal cord cultures (Masurovsky et al., 1981a,b, 1983; Letourneau and Ressler, 1984; Roytta et al., 1984; Letourneau et al., 1986). Taxol also inhibits the regenerative response of axons and Schwann cells after nerve crush injuries (Vuorinen et al., 1988a,b). Neurotoxicity has not been observed in phase I studies of taxol administered on single dose, multiple dose, or 3 hr infusional schedules (Ohnuma et al., 1985b; Legha et al., 1986; Grem et al., 1987). Although peripheral neurotoxicity has frequently occurred with 6 and 24 hr infusions, it has been rare at doses below 170 mg/m^2 (Donehower et al., 1987; Wiernik et al., 1987a,b; Rowinsky et al., 1989; Brown et al., 1991). In general, the incidence and severity of peripheral neurotoxicity has been dose-related. In a phase I study of taxol administered over 24 hr to solid tumor patients, neurotoxicity, as well as neutropenia, precluded dose escalation above 275 mg/m^2 (Wiernik et al., 1987a). However, in a study in refractory leukemias, all patients treated with doses of 315 to 390 mg/m^2 over 24 hr complained of mild to moderate paresthesias and numbness, but neurotoxicity was not the principal dose-limiting non-hematological toxicity (Rowinsky et al., 1989).

Taxol-related peripheral neurotoxicity has been principally characterized by neurosensory manifestations. The most common symptoms have been numbness and paresthesias in a glove-and-stocking distribution. Perioral numbness has also been described. Symptoms have begun as early as 24 to 72 hr after treatment with higher doses ($\geqslant 250$ mg/m^2), but symptoms have also occurred after multiple courses at lower doses. Neurotoxic manifestations have been cumulative and have progressively worsened after multiple courses at higher doses. Initially, most patients have complained of a burning pain, particularly in the feet. The pain has often been associated with hyperesthesias. Neurologic examinations have revealed distal sensory loss to large (proprioception, vibration) and small (pin prick, temperature) fiber modalities (Donehower et al., 1987; Wiernik et al., 1987a,b; Lipton et al., 1989; McGuire, S. A. et al., 1989; Rowinsky et al., 1989). Loss or decreased distal deep tendon reflexes has also been common in patients with neuropathic complaints. Lipton et al. (1989) have reported electrophysiologic findings in several symptomatic patients including decreased nerve conduction velocities in sensory nerves with relative sparing of motor nerves. Significant elevations in vibratory and thermal threshold elevations have also been noted (Wiernik et al., 1987a,b; Lipton et al., 1989). These electrophysiologic data have supported both axonal degeneration and demyelination as mechanisms for taxol-induced neurotoxicity (Lipton et al., 1989).

Sensory symptoms have usually improved or resolved within several months after discontinuation of taxol (Donehower et al., 1987; Wiernik et al., 1987a,b; Rowinsky et al., 1989). Areflexia has also

been noted to resolve completely (Wiernik *et al.*, 1987b). In one report, a sural nerve biopsy performed on a patient with severe neurotoxic symptoms that did not resolve completely after treatment, revealed no disarray or aggregation of microtubules in axons or Schwann cells (Wiernik *et al.*, 1987b). Instead, it showed thinly myelinated axons suggesting remyelination. Amitriptyline has been found by some investigators, but not others, to be useful in ameliorating residual neuropathic symptoms (Wiernik *et al.*, 1987a; Rowinsky *et al.*, 1989). Interestingly, nerve growth factor, a neuronotrophic factor required for maintenance of sympathetic and dorsal root ganglion cells in culture, has been shown to attenuate the microtubule disrupting effects of taxol in organotypic cultures (Peterson and Crain, 1982; Crain and Peterson, 1984).

Although taxol-induced motor disturbances have generally been absent or mild, severe motor dysfunction has also been reported. Severe generalized weakness that briefly prevented ambulation and transient paralytic ileus have been described in two diabetic patients following 24 hr infusions of taxol at 250 mg/m^2 (Wiernik *et al.*, 1987b). In addition, mild lower extremity motor dysfunction has been described in a refractory leukemia patient who received three 24 hr infusions of taxol administered over 24 hr at doses of 200 to 315 mg/m^2 (Rowinsky *et al.*, 1989).

Risk factors for the development of peripheral neurotoxicity such as previous therapy with other neurotoxic chemotherapeutics have been evaluated in a phase I trial (Donehower *et al.*, 1987). In the study, 18 patients received potentially neurotoxic doses of taxol ranging from 170 to 265 mg/m^2 over 6 hours. Of the 11 patients in the group who previously received cisplatin or vinca alkaloids, 9 developed symptomatic neurotoxicity. Seven patients received no prior neurotoxic therapy, but 5 still developed neuropathic effects. McGuire and colleagues also reported that multiple courses (1 to 20) of taxol induced either no or mild neuropathic symptoms in the majority of ovarian cancer patients who had been heavily-pretreated with cisplatin-based chemotherapy (McGuire, W. P. *et al.*, 1989). However, the extent of prior chemotherapy and neutropenia limited taxol doses during most courses in that trial to 110–170 mg/m^2. Neurotoxicity was evaluated prospectively in a phase I study of taxol and cisplatin at Johns Hopkins in which rigorous sequential neurological and neurometric examinations were performed; neurotoxicity was mild and infrequent even after multiple courses of cisplatin (50–75 mg/m^2) and taxol (110–200 mg/m^2) with the exception of 3 patients with histories of substantial alcohol use who developed moderate neurosensory toxicity.

Transient myalgias and arthralgias have also been observed with higher taxol doses and prolonged infusion durations (Donehower *et al.*, 1987; McGuire, W. P. *et al.*, 1989; Rowinsky *et al.*, 1989). These symptoms have occurred 2 to 3 days after treatment and resolved within 5 days. Severe myalgias and arthralgias requiring narcotics for palliation have also been observed with higher doses (315 to 390 mg/m^2) (Rowinsky *et al.*, 1989). Signs of inflammation and elevations in muscle enzymes such as creatine phosphokinase have not been noted (McGuire, W. P. *et al.*, 1989). Grand mal seizures have also been noted during taxol infusions administered to patients with and without evidence of organic brain dysfunction (McGuire, W. P. *et al.*, 1989; Brown *et al.*, 1991).

3.1.8.5. *Cardiac toxicity.* Cardiac disturbances associated with taxol have recently been reviewed (Rowinsky *et al.*, 1991b). Transient asymptomatic bradycardia has frequently been noted during taxol infusions in patients without cardiac risk factors. Asymptomatic bradycardia has occurred in at least 1 course administered to 29% of ovarian cancer patients (McGuire, W. P. *et al.*, 1989; Rowinsky *et al.*, 1991b) and is probably not an indication for discontinuing taxol. However, two patients have developed more significant bradyarrythmias that have been temporarily related to taxol including 1 patient who developed a progressive atrioventricular block that culminated in third degree block and 7 sec of asystole in 1 patient (McGuire, W. P. *et al.*, 1989; Rowinsky *et al.*, 1991b). Although the patient remained asymptomatic, a pacemaker was inserted and subsequent taxol infusions were associated with capture of paced beats when the sinus rate fell below the demand rate. This rhythm reverted to an unpaced rhythm following each taxol infusion. A second patient developed a 2:1 block during each of several courses that resolved within hours after taxol. Although it is uncertain whether taxol or its cremophor vehicle are directly responsible for these bradyarrythmias, taxol has been suspected since other agents formulated in cremophor have not been associated with similar arrhythmias.

Although ventricular tachycardia has not been observed during phase I and II trials of taxol despite intensive cardiac monitoring, short episodes of ventricular tachycardia have occurred in 4 patients who were monitored during taxol infusions in a phase I study of cisplatin and taxol (Rowinsky *et al.*, 1991a,b). Outpatient Holter recordings, which were performed to assess baseline cardiac rhythms, were unremarkable in four of the 5 patients. While the number of events is small enough that this may be coincidental, it raises the question of a synergistic effect of cisplatin and taxol on the myocardium. Several patients have also complained of atypical chest pains during taxol infusions which may have actually been manifestations of HSRs (Donehower *et al.*, 1987; Weiss *et al.*, 1990). However, a fatal myocardial infarction that was confirmed on postmortem examination and not preceded by an arrhythmia has also occurred during an infusion of taxol given to a patient with atherosclerotic cardiovascular disease

(Rowinsky *et al.*, 1991a,b). Although these cardiac events have occurred infrequently, they are of significant concern in light of anticipated broad phase II evaluation.

3.1.8.6. *Miscellaneous*. Alopecia has been observed in almost all patients treated with taxol at doses $\geqslant 135$ mg/m^2. Like alopecia due to other antineoplastic agents, taxol-induced alopecia has been reversible, but it has also been unique in other respects. The loss of scalp hair, which has generally occurred between days 14 and 21, has been sudden and complete, often occurring in a single day. In addition, patients have often experienced a loss of all body hair including axillary pubic and extremity hair, eyelashes, and eyebrows.

Other drug- or cremophor-related effects have included local venous toxicity with erythema, tenderness, and discomfort along the course of an injected vein and cellulitis and erythema without ulceration in areas of dermal extravasation. Fatigue, headaches, taste alterations, and minor elevations in hepatic and renal functions have also been noted infrequently in patients with progressive cancer. In addition, taxol has also been noted to produce significant elevations in serum triglycerides (Kris *et al.*, 1986).

3.2. TAXOTERE (RP 56976)

Recently, a semisynthetic taxol analog taxotere (RP 56976; *N*-debenzoyl-*N*-tert-butoxycarbonyl-10-deacetyl taxol) (Fig. 4) was found to have significant potential as an antineoplastic agent. Taxotere is of special interest not only because of its antineoplastic activity but because it precursor, 10-deacetyl baccatin III, has been isolated from the leaves of *Taxus baccata*, which can regenerate. In addition, an OC(CH3)$_3$ moiety replaces a benzamide phenyl group on the C-13 side chain of taxotere and a hydroxy group replaces an acetyl group which renders taxotere approximately 25% more water soluble than taxol (Ringel and Horwitz, 1991). Taxotere has been demonstrated to be even more potent than taxol in

polymerizing tubulin in the absence of GTP (Barasoain *et al.*, 1991; Ringel and Horwitz, 1991). Similar to taxol, taxotere stabilizes microtubules against depolymerizing agents such as calcium and low temperatures and induces microtubule bundle formation in cells (Barasoain *et al.*, 1991; Ringel and Horwitz, 1991). Taxotere has demonstrated impressive activity in many murine tumor models including B16 melanoma and advanced colon 38, and pancreatic PO3 adenocarcinomas (Lavelle *et al.*, 1989; Bissery *et al.*, 1990, 1991). Taxotere was also significantly more active than taxol against P388 murine leukemia and the mouse macrophage-like cell line J774.2, and at least 5-fold more potent in its taxol-resistant variant J7.TAX-50 (Ringel and Horwitz, 1991).

Pharmacokinetic studies performed in mice bearing colon 38 tumors have demonstrated that drug disposition is biphasic with alpha and beta $t_{\frac{1}{2}}$ of 0.1 and 1.1 hr, respectively; AUC have been proportional to dose indicating linear pharmacokinetics (Bissery *et al.*, 1991). In addition, tissue distribution studies at the MTD have indicated that taxotere concentrations in colon 38 are greater than accumulation in spleen, lung, kidney, heart, muscle, liver, and plasma at 24 hr after drug administration.

Phase I evaluations of taxotere formulated in ethanol and polysorbate 80 have recently begun in Europe and the United States (Extra *et al.*, 1991).

3.3. NOVEL ANTIMICROTUBULE AGENTS IN PRECLINICAL DEVELOPMENT AND CONCLUSION

Although the clinical development of antimicrotubule agents has been relatively static over the last several decades, there has been a recent resurgence of interest in these agents. This has primarily been due to the exceptional clinical antitumor activity demonstrated for both new analogs such as NVB and a new class of antimicrotubule agents, the taxanes, which posses a novel mechanism of cytotoxic action. Over the next several years, the clinical potential of these agents will be fully explored. In addition, a renewed appreciation of the clinical utility of antimicrotubule
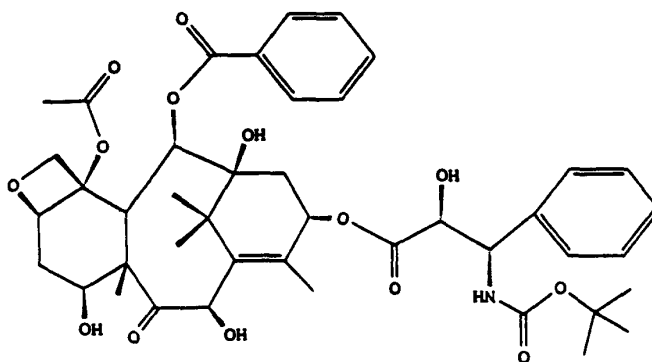

FIG. 4. Structure of taxotere.

agents as well as improved techniques to extract, screen, and produce clinically relevant quantities of natural products has recently resulted in the evaluation of other antimicrotubule agents such as estramustine (Tew and Sterns, 1989), rhizoxin (Tsuruo et al., 1986; Takahashi et al., 1987; Graham et al., 1991), and the dolastatins (Bai et al., 1990).

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