Chapter 2

Clinical Utility of Vincristine in the Treatment of Human Carcinomas

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Abstract

Vincristine is a naturally occurring alkaloid derived from the leaves of Cantharanthus roseus with a potent clinical activity against a wide variety of human carcinomas. The medicinal values of vincristine have been known since from the 17th century. However, its first successful clinical use was reported in 1962 for the treatment of acute leukemia. Subsequently, vincristine has become an integral part of chemotherapy regimens for the treatment of a variety of cancers. Currently, vincristine plays a key role in the treatment of hematologic malignancies and solid tumors. It induces cytotoxicity through the interference with microtubule formation and mitotic spindle dynamics, as well as the disruption of intracellular transport and decreased tumor blood flow with the latter probably as a consequence of anti-angiogenesis. The antitumor activity of vincristine is dependent on dose and duration of exposure. Vincristine

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binds to spindle microtubules and disrupts spindle structure and function in a dose dependent manner. However, this cytotoxic drug has several pharmacological limitations.

It has a bi-exponential pharmacokinetic profile with a very short and extensive initial distribution half-life followed by a longer elimination half-life. In addition, vincristine has a large volume of distribution, suggesting diffuse distribution and perhaps extensive tissue binding. These pharmacological properties may limit its optimal clinical benefit by limiting plasma and cancer tissue maximum concentration and cancer tissue drug exposure. Cytochrome P450 enzymes and concomitant drugs such as corticosteroids and other drugs are known to influence the vincristine pharmacokinetics.

Clinically, vincristine is administered intravenously as an infusion for the treatment of various cancers. Early studies using a single-agent therapy reported mixed findings on the effectiveness of vincristine. In children with relapsed acute lymphoblastic leukemia (ALL), vincristine monotherapy resulted in 50% complete remission rates. However, other studies indicated that vincristine had no advantage over a placebo in remission maintenance. When administered in association with prednisolone, vincristine improved the disease-free survival of children with ALL.

Currently, vincristine is a critical component of various chemotherapy regimens for the treatment of Hodgkin's lymphoma, non-Hodgkin's lymphoma, ALL, and nephroblastoma. It is used in combination with prednisone to treat childhood leukemia. Vincristine is also used in combination with dexamethasone and L-asparaginase for the treatment of ALL.

Despite numerous studies, vincristine dosing in multi-agent chemotherapy is not fully understood. The dose limiting toxicity of vincristine consists of a peripheral neuropathy characterized by progressive motor, sensory, and autonomic involvement in varying combinations. To optimize its therapeutic index, liposomal vincristine formulation has been developed and is currently being evaluated in clinical trials. Recently, the liposomal vincristine formulation received accelerated approval by the United States Food and Drug Administration (FDA) for a narrow indication: the treatment of adult patients with Philadelphia chromosome (Ph)-negative ALL in second or greater relapse that has progressed after 2 or more lines of anti-leukemia therapy.

In addition, multi-modality regimens containing liposomal vincristine formulation are clinically effective in patients with non-Hodgkin’s lymphoma. New clinical research efforts to maximize the therapeutic ratio of liposomal vincristine formulations are being explored and several clinical trials are underway to evaluate the clinical effectiveness of liposomal vincristine for the treatment of a variety of cancers.
Clinical Role of Vincristine

Introduction

Vincristine remains a potent and widely used anti-tumor agent for the treatment of a variety of neoplasms including acute lymphoblastic leukemia (ALL), Hodgkin’s disease, non-Hodgkin’s lymphomas (NHL), multiple myeloma, neuroblastoma, breast cancer, urothelial carcinoma, soft tissue sarcomas, Wilms’ tumor, and small cell and non-small cell lung cancers (Boman et al., 1998; Waterhouse et al., 2005). It is also used in some non-malignant conditions, such as idiopathic thrombocytopenia and hemangiomas (Ahn et al., 1974; Moore and Pinkerton, 2009). Vincristine received its first approval by the United States Food and Drug Administration (FDA) in 1963, under the trade name Oncovin, at a dose of 1.4 mg/m² for the treatment of acute leukemia in children (Liesveld and Asselin, 2013; Waterhouse et al., 2005). Since then, Vincristine has become one of the most commonly used antitumor drugs. Vincristine is rarely used as a single agent for the treatment of cancer. However, this cytotoxic agent is an essential component of other chemotherapy regimens; for instance, Cyclophosphamide, Hydroxydaunorubicin, Oncovin (vincristine), Prednisone or Prednisolone (CHOP) for the treatment of lymphomas (Shipp et al., 1995; Tirelli et al., 1998). Thus, this cytotoxic drug remains a universal component of induction therapy, intensification (remission consolidation), remission maintenance, and salvage therapies for ALL. Although vincristine has a broad spectrum of applications and history of clinical use for more than 50 years, much remains unknown about this important cytotoxic drug.

History of Vincristine

Vincristine is a member of the vinca alkaloids family of anti cancer agents. It has potent clinical activity against a wide variety of human carcinomas. It is a naturally occurring alkaldoid extracted from the leaves of widely cultivated white- or pink-flowered Madagascar periwinkle plant Catharanthus roseus (formerly known as Vinca rosea Linn) (Johnson et al., 1963; Svoboda et al., 1962). Vincristine is a vesicant which means it can cause serious damage to the tissue if the medication leaks out of the vein. Although vincristine was introduced successfully as a cytotoxic agent in 1962, its medicinal values have been described since the 17th century (Gidding et al., 1999a; Moore and Pinkerton, 2009).
In folklore medicine, the medicinal values of the extracts from the plant *Catharanthus roseus* have been described as being effective for the treatment of hyperglycemia, hemorrhage, scurvy, toothache, wound healing, and diabetic ulcers (Cervantes et al., 1980; Nayak and Pinto Pereira, 2006; White, 1925). These medicinal uses of the *Catharanthus roseus* described in folklore medicine have led to the screening of various fractions of this plant's extracts for their hypoglycemic activity, which turned out to be of little importance. Although vincristine was found to be an ineffective oral anti-diabetic drug, the periwinkle extract was effective in inhibiting leukocyte production and maturation (Johnson et al., 1963; Noble, 1990; Sampey, 1964; Silverman and Deitcher, 2013). Further research revealed that vincristine was one of the few clinically valuable extracts of the *Catharanthus roseus* (Neuss et al., 1964; Noble et al., 1958). The first successful clinical use of vincristine, then called leurocristine, was reported in 1962 for the treatment of acute leukemia (Costa et al., 1962; Karon et al., 1962). Subsequently, vincristine has become an integral part of chemotherapy regimens for the treatment of a variety of cancers.

**Molecular Characteristics of Vincristine**

In general, the vinca alkaloids including vincristine have a large dimeric asymmetric structure (Figure 1) composed of a dihydroindole nucleus (vindoline), which is the major alkaloid in the periwinkle, linked by a carbon-carbon bond to an indole nucleus (catharanthine), which is found in much lower quantities in the plant. During the extraction from *Catharanthus roseus*, sulphate salt is added at the ratio of 1:1 to yield vincristine sulphate. The molecular characteristics of vincristine are listed in Table 1. The molecular formula of vincristine sulphate is \( \text{C}_{46}\text{H}_{56}\text{N}_{4}\text{O}_{10}\text{H}_{2}\text{SO}_{4} \) and its molecular weight is 923.1 kDa. Vincristine sulphate is soluble in water (1 in 2), ethanol (1 in 600), chloroform (1 in 30) and methanol (Knottnerus, 2007). In its pure form, vincristine is a solid white to off-white powder with a melting temperature between 218°C and 220°C (Waterhouse et al., 2005). In its solid white to off-white powder form, vincristine is stable for 2 years at -20°C, but in the soluble form (dissolved in dimethyl sulfoxide), it is stable for one week at -4°C and one month at -80°C (Knottnerus, 2007). Vincristine is sensitive to hydrolysis, oxidation and heat. It is a lipophilic amine, a weak base, with \( pK_a \)s at 5.0–5.5.
and 7.4 and a partition coefficient (P) between octanol and water of log \( P = 2.82 \) (Leo et al., 1971).

![Molecular Structure of Vincristine](image)

**Figure 1. Molecular Structure of Vincristine.**

**Table 1. Key Properties of Vincristine**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>( \text{C}<em>{46}\text{H}</em>{56}\text{N}<em>{4}\text{O}</em>{10}\text{H}<em>{2}\text{SO}</em>{4} )</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>923.1 kDa</td>
</tr>
<tr>
<td>Melting temperature</td>
<td>218°C - 220°C</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Low concentrations inhibit microtubule dynamics (dynamic instability and treadmilling) High concentrations inhibit polymerization of tubulin</td>
</tr>
<tr>
<td>Standard dosage</td>
<td>1.0 to 1.4 mg per m(^2) every week</td>
</tr>
<tr>
<td>Administration</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>Principal toxicity</td>
<td>Peripheral neurotoxicity</td>
</tr>
<tr>
<td>Other toxicities</td>
<td>Infusion site reactions, constipation,</td>
</tr>
<tr>
<td>Precaution</td>
<td>Patients with abnormal liver function should be treated with caution.</td>
</tr>
<tr>
<td>Indication</td>
<td>Leukemia, Hodgkin’s and NHLs, multiple myeloma, neuroblastoma, breast cancer, urothelial carcinoma, soft tissue sarcomas, Wilms’ tumor, and small cell and non-small cell lung cancers</td>
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**Clinical Pharmacology of Vincristine**

Despite significant advances, the pharmacokinetics of vincristine is not well established. Since the drug is poorly absorbed if administered orally, it is
administered intravenously as a bolus injection (push from a syringe over approximately 5 minutes) or as an infusion from a mini-bag over approximately 10 minutes. Earlier studies have been evaluated the pharmacokinetics of vincristine in both pediatric and adult patients. After an intravenous injection, the pharmacokinetics of vincristine are characterized by large inter- and intra-patient variations in parameters such as clearance, volume of distribution, and elimination half-life (Gidding et al., 1999a).

Following an intravenous bolus administration, vincristine has a rapid initial decline in plasma concentrations (initial half-life of 5 to 10 minutes), followed by a prolonged terminal elimination phase with a half-life of more than 12 hours (Crom et al., 1994; de Graaf et al., 1995; Rahmani and Zhou, 1993; Sethi et al., 1981; Sethi and Kimball, 1981). This reflects the rapid cellular uptake and extensive tissue binding of vincristine after an intravenous injection. Peak plasma concentrations of 100 - 400 nM are briefly achieved with the t$_{1/2a}$ (initial or elimination half-life) of approximately 8 minutes due to the rapid cellular uptake and extensive tissue binding of the drug (Moore and Pinkerton, 2009).

Indeed, in most pediatric patients the plasma levels of vincristine fall below 5 nM by 60 minutes with the long t$_{1/2b}$ (half-life of the terminal phase of elimination) of over 14 hours indicating that plasma levels of 1 - 2 nM are maintained for relatively long periods of time (de Graaf et al., 1995; Moore and Pinkerton, 2009).

In general, the clearance of vincristine is greater in children compared with infants; however, it is not very clear whether there is an association of vincristine clearance with age during childhood (Crom et al., 1994; Gidding et al., 1999b). Moreover, no clear relationship exists between systemic exposure of vincristine and its toxicity.

Vincristine clearance is more rapid in children than in adults, and adults have a more than 2 fold longer terminal half-life (Crom et al., 1994; de Graaf et al., 1995). The cerebrospinal fluid (CSF) penetration of vincristine is yet to be determined in children, but in adults the vincristine levels of the CSF are 20 to 30 fold lower compared with concurrent corresponding plasma concentrations (Rowinsky and Donehower, 1996). Liver metabolism and biliary excretion are the principal routes for elimination of vincristine. Studies using radiolabeled dose of vincristine reveal that 70% to 75% of the radioactivity appears in the feces by 72 hours, and 10% of the radioactivity is excreted in the urine (Bender et al., 1977; Jackson et al., 1978; Owellen et al., 1977). Half of the radiolabeled material in urine and feces represents

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metabolites. The metabolism of vincristine and other vinca alkaloids is mediated by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily.

Evidence from multiple studies concluded that the CYP3A family of enzymes is responsible for the metabolism of the vinca alkaloids (Dennison et al., 2007; Dennison et al., 2006; Gidding et al., 1999a). CYP3A5 is believed to mediate 80% of the CPY3A metabolism of vincristine for individuals with high CYP3A5 expression, which may in part explain the large inter-patient variability in vincristine pharmacokinetics (Dennison et al., 2008).

Clinical Use of Vincristine

Since its introduction in 1963, vincristine sulfate, commonly known as vincristine, has been widely used as a therapeutic agent in both malignant and non-malignant diseases.

Vincristine Use in Malignant Disease

Vincristine has been used for a variety of malignancies including acute ALL, Hodgkin’s and NHLs, multiple myeloma, neuroblastoma, breast cancer, urothelial carcinoma, soft tissue sarcomas, Wilms’ tumor, and small cell and non-small cell lung cancers. Vincristine has been used more frequently and more effectively in children than in adults with cancer. This could be due to the fact that vincristine exhibits a higher level of sensitivity and better tolerance with relatively higher doses in pediatric patients than in adult patients.

Vincristine Monotherapy for Malignant Disease

Early studies have focused mostly on the single agent activity of vincristine in various malignancies (Table 1). Research supporting the activity of single agent vincristine therapy was mostly performed in the 1960s and early 1970s.

In the pediatric oncology setting, vincristine was first used as a single agent therapy with high response rates in the 1960s for childhood malignancies that were refractory to conventional therapy consisting of steroids, methotrexate, mercaptopurine, and alkylating agents. In general, its
clinical effectiveness was stronger in hematological malignancies compared with the solid tumors.

However, the responses were often incomplete and remissions were mostly brief (DeConti and Creasey, 1975; Livingstone and Carter, 1970). In adult oncology, vincristine was first used as a single agent therapy during the 1960s for neoplasms that were refractory to other agents. Similar to the pediatric oncology setting, the clinical effectiveness of vincristine was higher in hematological malignancies than those of solid tumors (DeConti and Creasey, 1975; Livingstone and Carter, 1970).

Combination Chemotherapy with Vincristine

Currently, vincristine is part of multi-agent or multi-modality chemotherapy regimens used in treating many childhood hematological and solid malignancies (Rowinsky and Donehower, 1991). Vincristine continues to be an important component of multi-agent chemotherapy regimen with high response rates in pediatric blood cancers such as ALL, NHL or Hodgkin’s disease. Vincristine combined with actinomycin-D has been used successfully in children with Wilms’ tumors (D’Angio et al., 1976). In addition, vincristine is routinely used as a part of multimodality therapy in the front-line treatment of rhabdomyosarcoma, Ewing sarcoma, and neuroblastomas in children. Furthermore, Vincristine has been used effectively in the treatment of brain tumors in pediatric patients. Moreover, vincristine in combination with other active drugs is clinically effective for the treatment of childhood retinoblastoma (Doz et al., 1994; Pratt et al., 1985).

Although vincristine plays a limited role solid malignancies in adults, it is a component of multi-modality chemotherapy regimens in treating newly-diagnosed ALL in adult patients (Rowinsky and Donehower, 1991). However, the clinical effectiveness of vincristine is relatively lower in adult ALL patients compared with the pediatric ALL patients (DeConti and Creasey, 1975). Vincristine combined with other chemotherapy drugs is effectively used in adult patients for the treatment of chronic myeloid leukemia (CML), and during their maintenance therapy (Griffin et al., 1983; Rosenthal et al., 1977). Among other vinca alkaloids, vincristine is used routinely in adult patients as a component of multi-modality chemotherapy regimen for Hodgkin’s disease (Rancea et al., 2013; Townsend and Linch, 2012). Vincristine in combination with other chemotherapy agents such as mechlorethamine, procarbazine, and prednisone was a significant
breakthrough that improved the survival outcomes for patients with advanced Hodgkin's disease (Straus, 1989).

Similarly, vincristine in combination with other chemotherapy agents is the treatment of choice for NHL in adults (Shankland et al., 2012). Over the years, vincristine has been used in combination with several chemotherapy agents in the treatment of progressive multiple myeloma in adults (Hansen et al., 1985; MacLennan and Cusick, 1985; San Miguel et al., 2012). A staged approach using vincristine combined chemotherapy with adriamycin and dexamethasone has proven to be effective in improving overall response rates and prolonging overall survival rates in newly diagnosed multiple myeloma patients (Chim et al., 2010). Vincristine in combination with melphalan, cyclophosphamide and prednisolone is effective in refractory or recurrent multiple myeloma (Kabir et al., 2012).

Vincristine is also a component of multi-modality chemotherapy regimens used for the treatment of several solid tumors (Aapro and Wildiers, 2013). In small cell lung cancer combination chemotherapy with vincristine and other agents produced similar survival rates compared with the newer regimens without vincristine (Bilgi et al., 2010; Pallis et al., 2010; von Pawel et al., 1999). Vincristine when combined with doxorubicin and ifosfamide has shown to be effective in the treatment of adult rhabdomyosarcoma (Hays, 1993; Ogilvie et al., 2010).

Vincristine is often included in the treatment of brain tumors in adults if combination chemotherapy is required, however, its effects on overall survival appear to be minimal (Fewer et al., 1972). In breast cancer treatment, the clinical effectiveness of vincristine is limited (Aisner et al., 1995; Lichtman et al., 1991; Segaloff et al., 1985).

In other solid tumors such as cervical carcinoma, non small cell lung cancer, and malignant melanoma, vincristine monotherapy was found to be clinically effective but appears to have no survival benefit when combined with other agents as a combination therapy. However, as a multi-drug chemotherapy, vincristine was used successfully in the treatment of AIDS associated Kaposi’s sarcoma (Gill et al., 1990; Gill et al., 1992; Kaplan et al., 1986).

**Vincristine Use in Non-Malignant Disease**

Vincristine has been used effectively in the treatment of hemangiomas, (including hemangioendothelioma and Kaposi form haemangioendothelioma),
particularly those complicated by the Kasabach–Merritt syndrome of thrombocytopenia and consumptive coagulopathy.

An enriched tubulin content of endothelial cells along with the proliferating nature of hemangiomas makes vincristine a logical agent to be used for the treatment of these lesions (Perez et al., 2002; Perez Payarols et al., 1995). Vincristine also has been used successfully for the treatment of thrombocytopenia (Bobbio-Pallavicini et al., 1994; Thabet et al., 2013).

**Vincristine Toxicity**

Since the mechanism of action of vincristine is not confined selectively to tumor cells, toxic adverse effects are inevitable in patients receiving vincristine treatment. The organs most affected by vincristine therapy are the nervous system structures, lungs, the liver, and the kidneys.

**Neurotoxicity**

Neurotoxicity is a dose-limiting toxicity of vincristine and occurs most commonly in patients who are receiving vincristine on a weekly treatment schedule. Vincristine induced neurotoxicity is characterized by peripheral, symmetric mixed sensory-motor, and autonomic polyneuropathy (Gidding et al., 1999a; Gomber et al., 2010; Kassem et al., 2011; Warrier et al., 1992). Manifestations of the peripheral sensory and motor neuropathy include loss of deep tendon reflexes, neurogenic pain (muscular cramping, jaw pain), paresthesias, and wrist and foot drop.

The primary neuropathological effects of vincristine include axonal degeneration and reduced axonal transport as a result of interference with the axonal microtubule functions. Cranial motor nerves may be affected, and autonomic nerve involvement may be responsible for constipation, paralytic ileus, and urinary retention (Dixit et al., 2012). In most cases, these symptoms are reversible on withdrawal of the drug (Kassem et al., 2011).

Several factors such as the patients’ age, the dosage regimen, and concomitant drug therapy, may contribute the incidence and severity of vincristine induced neuropathy. Hepatic dysfunction and obstructive liver disease also increases the risk of developing severe neuropathy (Rowinsky, 2003).
Other Toxicities of Vincristine

Hematological toxicity of vincristine is rare, however, mild and readily reversible myelosuppression with leukopenia and anemia have been previously reported in (Gidding et al., 1999a; Holland et al., 1973). Higher doses of vincristine have been shown to induce severe myelosuppression (Kaufman et al., 1976). In some cases, vincristine causes thrombocytopenia. Other adverse events reported in association with vincristine therapy include alopecia, myocardial infarction, gastrointestinal ulceration and necrosis with perforation, fever, and skin rash (Gidding et al., 1999a; Rowinsky and Donehower, 1991).

Inadvertent Intrathecal Vincristine

Inadvertent intrathecal administration of vincristine has been shown to be lethal in several cases (Reddy et al., 2011). When administered intrathecally, vincristine causes severe and irreversible central nervous system toxicity and motor dysfunction followed by progressive ascending radiculomyelo-encephalopathy, coma and death (Gilbar and Carrington, 2004). The true incidence of inadvertent intrathecal vincristine administration is not known. Some of these incidents, particularly lethal events, prompt publication and others are reported to organizations such as the Institute for Safe Medication Practices. Nearly all instances of inadvertent intrathecal vincristine administration have resulted in death within days despite therapy with an exception of one patient who was in a coma for one year. In other instances where treatment was administered immediately after an intrathecal injection of vincristine, patients have survived with paraparesis or tetraparesis following supportive care therapy. To our knowledge, there have been only 6 cases reported in the literature where a patient has not died as a consequence of this medication error (Reddy et al., 2011). Therefore, effective measures for prevention of these medication errors need to be developed and incorporated as worldwide standard practice.

Strategies to Reduce Vincristine Toxicity

Since vincristine has a very narrow therapeutic index with little separation between therapeutic and toxic doses, standard vincristine dose escalation could
not be achieved for its optimal use. Despite an approved dosage of 1.4 mg/m$^2$ for adult patients, most regimens with vincristine are routinely capped at 2.0 mg/m$^2$ to minimize vincristine induced neurotoxicity. Thus, this dose capping combined with the rapid plasma clearance limit vincristine’s delivery to the target tissues and its efficacy optimization regardless of the patients size. Moreover, dose-density and cumulative doses of vincristine increases the toxicity leading to dose reductions, dose delays or complete discontinuation of the drug in certain instances. Regardless of the dosing schedule, unacceptable toxicity associated with vincristine has prohibited dose escalation and target delivery to the tumor cells. To achieve the optimal dose delivery of vincristine to the tumor cells, liposomal formulations have been developed by encapsulating vincristine within the aqueous core of unique, nanoparticle, sphingomyelin and cholesterol liposomes. The liposomal formulation is distinct from alternate liposomes used in other approved pharmaceutical products and is uniquely suited to contain, deliver, and allow an increased dose intensification of vincristine. Compared to standard vincristine, the liposomal formulation of vincristine has a higher maximum tolerated dose, superior antitumor activity and higher amounts of active drug delivery to target tissues (Silverman and Deitcher, 2013).

An early phase I trial found that the maximum tolerated dose of sphingosomal vincristine was 2.4 mg/m$^2$. In a phase II trial, sphingosomal vincristine at a dose of 2.0 mg/m$^2$ was associated with dose limiting toxicities of pain and constipation (Gelmon et al., 1999). A review by Boehlke and Winter (Boehlke and Winter, 2006) included seven trials involving patients with ALL, Hodgkin disease, NHL, and solid tumors, the authors concluded that sphingosomal vincristine treatment resulted in an acceptable safety profile with better responses in heavily pre-treated patients. These authors also found excellent clinical outcomes in studies that used sphingosomal vincristine as part of a multi-drug regimen such as CHOP or Rituximab-CHOP (R-CHOP) therapy for NHL. Subsequently, Bedikian and coauthors (Bedikian et al., 2008; Bedikian et al., 2006) reported that vincristine sulphate liposome infusion at 2.0 mg/m$^2$ vincristine without an upper dose cap was well tolerated in 27 patients with metastatic melanoma.

On August 9, 2012, the FDA approved the vincristine sulfate liposome injection for weekly dosing at 2.25 mg/m$^2$ for the treatment of Philadelphia chromosome (Ph) –negative ALL. Recently, a pivotal phase II open-label trial by O’Brien et al. (O’Brien et al., 2013) demonstrated that vincristine sulfate liposome injection administered at 2.25 mg/m$^2$ weekly resulted in meaningful clinical outcomes including durable responses with an acceptable toxicity in
heavily pretreated adults with advanced, relapsed or refractory B-or T-lineage Ph-negative ALL. The most common adverse events associated with the vincristine sulfate liposome injection were febrile neutropenia, pyrexia, hypotension, respiratory distress, and cardiac arrest. A larger phase III confirmatory trial (HALLMARQ) is comparing the new liposomal product with standard vincristine in the front-line setting in adults with newly diagnosed Ph-negative ALL.

A pivotal phase II trial by Rodriguez et al. demonstrated that vincristine sulfate liposome injection administered at 2 mg/m$^2$, every 2 weeks, for a maximum of 12 cycles or until toxicity or disease progression was effective and tolerated safety in heavily pretreated patients who had aggressive NHL (Rodriguez et al., 2009).

Recently, a long-term phase II study by Hagemeister and co-investigators (Hagemeister et al., 2013) demonstrated that vincristine sulfate liposome injection, when substituted for non-liposomal vincristine in CHOP with or without rituximab, produced a response rate of 96% with an overall survival rate of 77% in patients with untreated aggressive NHL. Currently, vincristine sulfate liposome injection is being investigated in phase II trials of relapsed ALL, metastatic malignant uveal melanoma, and relapsed/ refractory NHL. In addition, a phase III trial of R-CHMP versus R-CHOP in elderly patients with untreated diffuse large B-cell lymphoma is ongoing.

**Conclusion**

Vincristine continues to be an integral component of multi-drug regimens for the treatment of a variety of cancers. However, its narrow therapeutic window and dose limiting toxicity of neuropathy has limited its potential leading to an empiric dose capping at 2.0 mg/m$^2$. Questions remain concerning the clinical scope of vincristine neuropathy. Thus, many patients with various malignant diseases receive sub-optimal doses of vincristine which may lead to poorer prognosis and outcomes for diseases where this agent plays a key role in the treatment of certain malignant diseases, especially ALL.

Despite the significant advances over the past decade, many questions and controversies surrounding vincristine dosing still persists. Clinical trials of multi-agent chemotherapy involving vincristine have not addressed its dosing. Many questions still remain regarding the clinical scope of vincristine induced neuropathy. The incidence of long-term sequelae is unclear as is the involvement of the central nervous system.
New clinical research efforts to maximize the therapeutic ratio of vincristine are being explored and vincristine sulfate liposome injection has been developed recently. Clinical trials are underway to evaluate the clinical effectiveness of liposomal vincristine for the treatment of a variety of cancers.

References


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Clinical Role of Vincristine


