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REVIEW

Vincristine sulfate liposomal injection for acute lymphoblastic leukemia

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Abstract: Vincristine (VCR) is one of the most extensively used cytotoxic compounds in hemato-oncology. VCR is particularly important for the treatment of acute lymphoblastic leukemia (ALL), a disease that accounts for approximately one-third of all childhood cancer diagnoses. VCR's full therapeutic potential has been limited by dose-limiting neurotoxicity, classically resulting in autonomic and peripheral sensory–motor neuropathy. In the last decade, however, the discovery that liposomal encapsulation of chemotherapeutics can modulate the pharmacokinetic characteristics of a compound has stimulated much interest in liposomal VCR (vincristine sulfate liposomal injection [VSLI]) formulations for the treatment of ALL and other hematological malignancies. Promising data from recent clinical trials investigating VSLI in adults with ALL resulted in US Food and Drug Administration approval for use in patients with Philadelphia chromosome (t[9;22]/*BCR–ABL1*) (Ph)-negative (Ph–) disease. Additional clinical trials of VSLI in adults and children with both Ph-positive (Ph+) and Ph– ALL are ongoing. Here we review the preclinical and clinical experience to date with VSLI for ALL.

Keywords: vincristine sulfate liposomal injection, liposomes, sphingosomal vincristine, acute lymphoblastic leukemia, chemotherapy

Introduction

Acute lymphoblastic leukemia (ALL) is a common hematological malignancy with an incidence of 1.7 per 100,000 per year across all age groups. Although the median age at diagnosis overall is 14 years, the peak incidence occurs in early childhood (2–5 years of age).[1] ALL comprises approximately 30 percent of all childhood cancers and has a male preponderance.[2,3] A diagnosis of ALL is usually made by documenting the presence of lymphoblasts in peripheral blood and/or >25% lymphoblasts in the bone marrow. Common presenting features are nonspecific, including fever, bone pain, lymphadenopathy, and anemia, and bleeding or bruising secondary to thrombocytopenia.[1]

The precise pathogenic events leading to the development of ALL are still unknown, although it is likely to arise from complex interactions between prenatal and postnatal exogenous and endogenous exposures, genetic susceptibility, and chance. Major cytogenetic and molecular genetic abnormalities seen in ALL include gene rearrangements and dysregulation, hyperdiploidy (>50 chromosomes), hypodiploidy (<44 chromosomes), and chromosomal translocations, of which t(12;21)(p13;q22) encoding *ETV6-RUNX1* is the most common. Certain chromosomal abnormalities in leukemic lymphoblasts disrupt genes that regulate normal hematopoiesis and lymphoid development, activate oncogenes, or constitutively activate tyrosine kinases. Several of

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these chromosomal rearrangements are significantly associated with clinical outcome and are used in the classification and risk stratification of leukemia.[1,4]

One archetypical genetic abnormality implicated in leukemogenesis is the Philadelphia chromosome (Ph), which arises from a balanced translocation between the long arms of chromosome 9 and 22 (t[9;22][q34;q11]), resulting in the fusion of the B-cell receptor (*BCR*) and the nonreceptor tyrosine kinase *ABL1* genes.[5] The reciprocal translocation results in the *BCR–ABL1* fusion product, leading to constitutive activation of ABL1 kinase following juxtaposition of BCR. The Ph is the characteristic cytogenetic feature of chronic myeloid leukemia (present in >90% of patients), but also occurs in ALL, with an age-related incidence ranging from 3% of patients under 20 years to 21% of cases over 50 years.[6]

Chemotherapy combined with tyrosine–kinase inhibitors such as imatinib mesylate (IM) induces complete remission (CR) in >90% of Ph-positive (Ph+) adults and children, many with undetectable minimal residual disease, translating to an overall survival rate of 50% in adults and event-free survival (EFS) of 88% in children.[7,8] In contrast, the CR and overall survival rates for adults with Ph+ ALL in the pre-IM era were <70% and 20%, respectively,[9] whilst the EFS for children was <45%.[7] In Ph-negative (Ph–) ALL, CR rates are 96%–99% in children and 78%–92% in adults.[1] However, there is a greater discrepancy in EFS, with rates approaching 90% for children compared with only 30%–40% in adults.[1] Standard treatment for ALL (Ph+ and Ph–) differs in adults and children, largely due to better tolerance of intensive multiagent chemotherapy in children. In both age groups, however, vincristine (VCR) is a key component of therapy.

Vincristine

VCR is a lipophilic amine, first introduced as an anticancer therapy over 45 years ago.[10,11] VCR is a cell cycle-dependent compound that directly binds to tubulin, causing microtubule depolymerization, M-phase arrest, and apoptosis in mitotic cells.[12] At low concentrations, VCR induces reversible mitotic arrest with little effect on morphology or polymerization of spindle microtubules.[13–15] In contrast, higher VCR doses and long-term VCR exposure are associated with microtubule depolymerization-induced cytotoxicity.[14–18] In addition, VCR impedes tumor blood flow, inducing tumor necrosis.[19] Although the role of microtubules in this process has not been fully elucidated, the efficacy of VCR for treating hemangiomas with high epithelial cell content[20] (thus high tubulin expression levels) suggests that the VCR mechanism of action against microtubule polymerization may play a role in the inhibition of tumor angiogenesis.[21] VCR also affects intracellular transport processes, which are thought to contribute less to its antineoplastic activity than to its modulation of microtubule polymerization.[19] However, it is the perturbance of these biochemical pathways that is predicted to mediate VCR-induced autonomic and peripheral sensory–motor polyneuropathy, a dose-limiting side effect of VCR.[22] The neurotoxic effects of VCR, mediated by impaired microtubule function leading to blockade of axon transport and subsequent axonal degradation, have significantly impaired the use of high-dose VCR in the treatment of neoplastic disease.[22] As a result, VCR doses are generally capped at 2 mg.[22] Therefore, there has been a recent impetus to enhance the therapeutic activity of VCR with liposomal encapsulation systems to increase the VCR dose whilst limiting free-drug-associated toxicity.

Liposomes

Lipids are naturally occurring amphipathic small molecules that are immiscible in aqueous solutions. When dispersed in aqueous solutions, the presence of a hydrophilic polar head group and hydrophobic apolar tail (Figure 1) induces a steric organization of phospholipids. As such, phospholipids spontaneously form bilayer membranes encapsulating ions or molecules present in the solution in which they are formed (Figure 1).[23] This functions to minimize the exposure to, and interaction of, the hydrophobic aliphatic chain with water. The amphiphilic nature of lipids induces the formation of liposomes, and contributes to the structural integrity of cell membranes as well as compartmentalization of cells into functional membrane-bound organelles.

Liposomes are multilamellar or unilamellar bilayer microspheres composed of lipids encapsulating an aqueous solution.[24] Importantly, liposome-enveloped substances are protected from enzyme-mediated degradation or inactivation by the immune system. Furthermore, liposomal encapsulation of drugs aims to enhance plasma concentration and circulation half-life, increase transport and accumulation within specific target tissues, and minimize toxicity.[25] These characteristics have led to the exploitation of liposomes in drug delivery. For example, liposomal encapsulation of VCR sulfate was recently approved by the US Food and Drug Administration as a therapeutic strategy for the treatment of Ph– ALL.

Early studies investigated the encapsulation of VCR within egg phosphatidylcholine (EPC)/cholesterol or

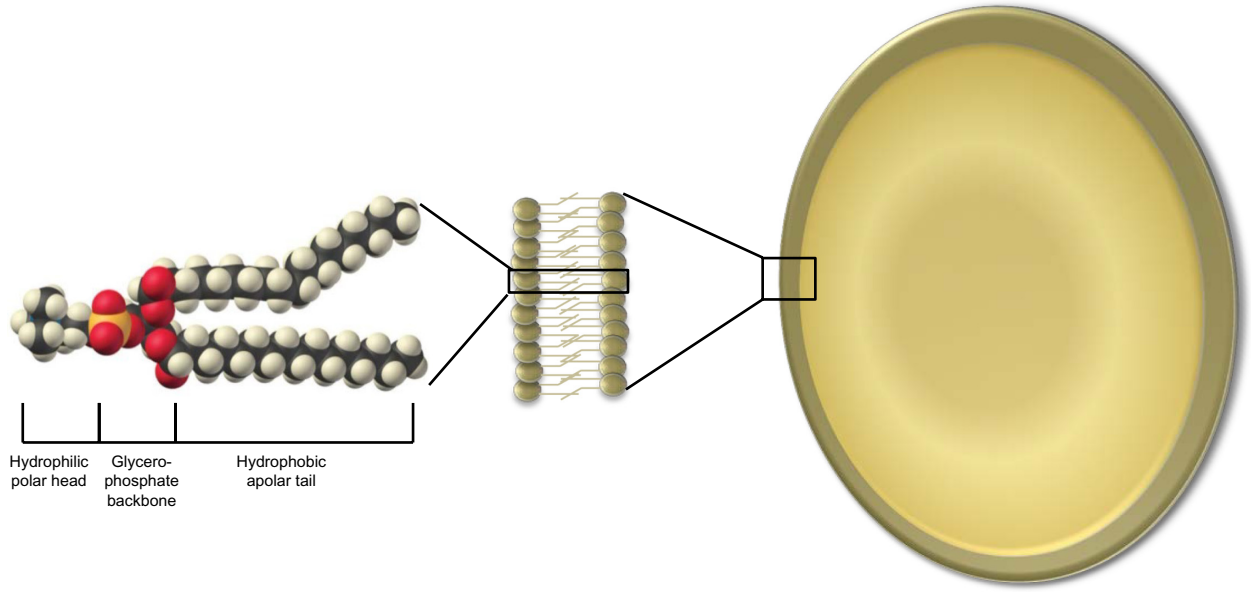

Figure 1 Phospholipids contain a glycerophosphate backbone covalently bonded to a polar head group and two fatty acyl tails. The bipolar nature of the phospholipid permits the formation of bilayer membranes in which proteins, cofactors, or chemical compounds such as vincristine can be encapsulated.

distearoylphosphatidylcholine (DSPC)/cholesterol liposomes, both at a concentration ratio of 55%:45%.[18] The inclusion of cholesterol acts to stabilize the liposome, preventing vesicle destabilization and concomitant drug release.[25] The drug uptake process can be driven by a pH gradient whereby the internal pH of the liposome is acidic at 4.0 while the external is slightly basic at pH 7.5.[26] Uptake efficiencies of up to 98% are achieved utilizing pH gradients, although disparity between the two liposomal formulations can occur. For example, VCR rapidly accumulates in EPC/cholesterol at 21°C, leading to >90% drug encapsulation after 30 minutes while entrapment of VCR in DSPC/cholesterol liposomes was only 17% under the same conditions. However, increasing the experimental temperature to 60°C enhanced entrapment to >98% after just 10 minutes.[26]

Just as the liposomal formulation affects VCR uptake, it can affect drug release. Under biologically relevant conditions, EPC/cholesterol liposomes release 96% of VCR into 37°C whole blood after just 24 hours. Due to the high membrane permeability of EPC liposomes, they are not commonly used in drug formulations today.[25] In contrast, DSPC/cholesterol liposomes release approximately 80% of VCR under the same conditions.[27] Importantly, the ability of the liposome to retain VCR correlated with the stability of the pH gradient, indicating that maintenance of the pH gradient magnitude across the vesicle membrane may be key to developing slow-release formulations of VCR from liposomes.

In vivo studies mimicked findings from in vitro work whereby VCR encapsulated in EPC/cholesterol liposomes leaked rapidly into the plasma following intravenous injection into mice.[27] Although substitution of EPC with DSPC enhanced the longevity of VCR retention within the liposome, improvements in in vivo retentions have also been achieved through manipulation of the intraliposomal pH concentration[28,29] or addition of the ganglioside GM1[28] or 5% polyethylene glycol.[30] The addition of polyethylene glycol chains provides a steric barrier around the liposome, which is predicted to protect the liposome from clearance by the patient's mononuclear phagocyte system, following opsonization of the liposome, and minimize interaction with serum proteins.[31] This, in turn, enhances circulation time and may alter the biodistribution of the liposome, to enhance tumor-specific liposome aggregation and functional interaction between the liposome and tumor cells.[25] Similarly, substitution of DSPC with sphingomyelin has been utilized in the encapsulation of VCR and exhibits the best retention properties such that up to 75% of encapsulated VCR remains within the liposome 24 hours following intravenous injection into mice in vivo.[28,32] As such, sphingomyelin liposomes are utilized in the encapsulation of VCR sulfate employed for the treatment of ALL and non-Hodgkin's lymphoma.

Liposomal vincristine sulfate injection

Vincristine sulfate liposomal injection (VSLI) (Marqibo®; Talon Therapeutics, Inc., South San Francisco, CA, USA) is

a sphingomyelin and cholesterol-based nanoparticle formulation of VCR sulfate. It was designed to deliver a larger dose of VCR directly to tumor cells via encapsulation within an aqueous core of nanoparticles comprising sphingomyelin and cholesterol liposomes, thereby avoiding undue neurotoxicity. A recent landmark study of VSLI monotherapy in adults with multiply relapsed or refractory Ph– ALL demonstrated an overall response rate of 35% and a composite CR rate of 20%.[33] In August 2012, the US Food and Drug Administration approved VSLI for the treatment of Ph– ALL in adult patients with progressive disease or second or greater relapse.

VSLI is a nanoparticle VCR formulation that encapsulates the compound in an aqueous core within a sphingomyelin/cholesterol liposome designated the nomenclature of Optisome™ (Talon Therapeutics, Inc.). Preclinical studies show that the sphingomyelin/cholesterol VCR formulation improves tumor drug exposure by enhancing drug delivery and tissue targeting.[32] Data from pharmacokinetic (PK) studies revealed that clearance of liposome-encapsulated VCR was slower than that for free VCR and was thought to contribute to the higher plasma concentrations observed over a longer time period for liposomal VCR.[34,35] For example, a preclinical model comparing conventional, aqueous VCR, DSPC/cholesterol, and sphingomyelin/cholesterol liposomal formulations showed that the encapsulated drug exhibited a significantly larger area under the concentration curve (AUC) (measure of bioavailability), a longer mean plasma residence time, and a lower volume of distribution.[35] Importantly, the progressive in vivo accumulation of VCR in tissues, based on maximum concentration (Cmax), demonstrates a preference for mononuclear phagocyte system tissues such as spleen, liver, lymph nodes, and bone marrow,[36] correlating to those tissues most affected by leukemic burden. Moreover, the specific efficacy of liposomal-encapsulated VCR is highlighted by the high concentration of VCR in tissue compared with the relatively low concentration of VCR within the plasma, suggesting that liposomal formulations result in little release of VCR in the peripheral blood but target encapsulated drug to the tumor.[35] Indeed, the in vivo tumor AUC value for sphingomyelin/cholesterol was over 120 times higher compared with nonliposomal VCR, and two-fold that of DSPC/cholesterol formulations.[35]

In human VCR studies, as for most anticancer drugs, intrapatient and interpatient PK profiles vary markedly.[22] For example, in a recent study of children, the median clearance, AUC, and Cmax of VCR were 482 mL/min/m^2 (range 132–698 mL/min/m^2), 49.7 mcg/L · h (16.5–143.1 mcg/L · h), and 3.5 mcg/L (1.0–31.2 mcg/L), respectively.[37] It is important to highlight that comparison between VSLI and VCR PK studies is difficult due to dose capping resulting from the neurotoxicities associated with free VCR compound. In contrast, VSLI studies are often reported with the absence of dose capping. The enhanced tissue targeting and drug delivery observed with liposomal formulations of VCR permit the administration of higher doses of VSLI compared with conventional administration of free compound.[38] For example, the conventional VCR dose of 1.5 mg/m^2 has a cap of 2.0 mg, limiting the dose for patients with a body surface area >1.33 m^2. However, there is no dose cap for the VSLI formulation.[39] In the Phase II Relapsed Acute Lymphoblastic Leukemia (RALLY) trial for VSLI treatment of Ph– ALL patients, the individual dose of VSLI ranged from 3.1 mg to 5.5 mg, up to 2.8-fold higher than the standard VCR dose. The weekly dose was fixed at 2.25 mg/m^2,[33,39] resulting in a cumulative dose range of 3.5–70.1 mg, much greater than that attainable with conventional VCR therapy.[33,39] Although the absence of dose capping makes comparison of PK between the VCR and VSLI formulations difficult, a recent study in patients with advanced solid tumors suggests that encapsulation of VCR improves PK. Patients treated with a single 2.0 mg/m^2 dose of the encapsulated VSLI formulation exhibited increased plasma AUC and decreased clearance rates compared with those treated with 2.0 mg/m^2 of conventional VCR.[34] Interestingly, variation of VSLI dose (1.5, 2.0, or 2.3 mg/m^2) or number of doses (1.5 or 1.8 mg/m^2 weekly for four cycles) did not significantly alter the PK of VSLI in these patients.[34] However, it should be noted that the patients in this study were Chinese and exhibited lower AUC and Cmax at a VSLI dose of 2.0 mg/m^2 compared with previous studies,[40,41] suggesting that pharmacogenomics may contribute to the PK of VSLI.

Efficacy

The first published Phase II clinical study of single-agent VSLI reported 16 adults (median age 35 years, range 23–64 years) with recurrent or refractory ALL, in whom the estimated likelihood of achieving CR was 30%–40% for 19% of the studied patients, and <10% for the remaining patients.[42] Pre-existing grade 1–2 neuropathy was permitted for the trial. VCR sulfate was encapsulated with sphingomyelin and cholesterol liposomes with sodium phosphate to produce a sphingosomal VCR mixture at a dose of 0.16 mg/mL. This VSLI mixture was administered by intravenous infusion over 60 minutes within 8 hours of preparation at a dose of 2.0 mg/m^2. This dose was repeated every 14 days in the absence of rapid disease progression or dose-limiting toxicities with the median number of doses of VSLI being

two (range one to five). Dose decrements of 0.2 mg/m^2 were implemented for nonhematologic toxicities of grade 3–4 severity. Premedication with antiemetics and adjuvant aperients were used to decrease adverse effects. Two patients were unevaluable for response due to the coadministration of other chemotherapy agents. Of the 14 evaluable patients, two (14%) had an overall objective response. This comprised one CR after three VSLI doses and a partial response with two VSLI doses. Both of these patients were Ph+. Another six Ph+ patients did not show a response. The remaining six evaluable patients were resistant to treatment with VSLI, although two showed transient reductions in bone marrow infiltrate prior to developing progressive disease.[42]

In the landmark Phase I trial of VSLI in advanced, relapsed, or refractory Ph− adult ALL, 65 patients aged ≥18 years were treated, with several durable responses seen.[33] Patients with residual persistent grade 1 or nonpersistent grade 2 or higher VCR-related neuropathy were included. Patients received weekly VSLI at 2.25 mg/m^2 with no dose capping, administered intravenously over 60 minutes. The primary efficacy end point was the proportion of patients who achieved CR or CR with incomplete recovery of peripheral blood neutrophil counts or platelet counts (CRi). An overall response rate of 35% was found, with 20% achieving either a CR or a CRi. CR/CRi was achieved in 25% of patients with an untreated relapse and 14% of those with relapse previously refractory to single-agent or multiagent antileukemic therapy. There was an associated survival benefit of 7 months in responders compared with 3 months in nonresponders.[33] These results are particularly significant given that this was a population of patients with heavily pretreated and advanced disease. Furthermore, 12 (19%) VSLI-treated patients proceeded to hematopoietic stem cell transplantation.[33]

Safety and tolerability

VSLI appears to be well tolerated and safe, even at doses exceeding the 2 mg maximal dose commonly applied to free VCR. Clinical experience with specific toxicities is summarized as follows.

Neuropathy

In the Phase II trial of VSLI reported by Thomas et al,[42] 16 patients received a median number of two doses, at a median dose of 3.8 mg (range 2.9–4.2 mg). Neurological assessments were performed prior to each dose of VSLI, with minimal neurotoxicity seen. Two patients were found to have grade 1 peripheral neuropathy after two and four doses of VSLI, both with a prior history of VCR-related peripheral neuropathy. Grade 2 orthostasis and intermittent headaches were seen in one patient. No significant unexpected toxicity was observed in the remaining patients.[42]

O'Brien et al[33] reported the use of VSLI doses of 2.25 mg/m^2 with no dose capping, with patients receiving a median of four doses of VSLI (range one to 18) and a median individual dose of 4.12 mg (range 3.14–5.51 mg). Neuropathy-associated adverse events were reported in 86% of the 65 patients evaluated. Grade 3 peripheral neuropathy-related events combined were reported in 23% of patients. However, 77% of patients had reported neuropathy-related signs or symptoms prior to the commencement of VSLI, consistent with prior VCR exposure. Higher grades of peripheral neuropathy were related to VSLI dose and response. Overall, VSLI produced no new or unexpected toxicities and showed a toxicity profile comparable with standard VCR at its labeled dose.[33]

Autonomic neuropathy and constipation

In addition to peripheral neuropathy, VCR has also been shown to cause autonomic neuropathy with secondary delayed gastric emptying, constipation, and bladder dysfunction.[43] Constipation has been reported in 34%–44% of patients with the use of VSLI. However, most of these have been of grade 1 and 2 severity.[33,44] In the landmark ALL study, only 3% of patients experienced constipation of grade 3 severity.[33]

Vesicant effect

Another significant risk of free VCR is its potential to cause tissue necrosis upon accidental extravasation. This risk has been shown to be significantly reduced with the use of liposomal VCR, with no gross inflammatory response seen on subcutaneous VSLI in mouse models. As extravasation following standard intravenous administration occurs in up to 1%–2% of chemotherapy infusions, this decreased risk of tissue necrosis is potentially clinically relevant.[18]

Hepatic dysfunction

Bedikian et al[41] studied the use of VSLI in seven patients with malignant melanoma and abnormal liver function. The VSLI was administered at a dose of 1.0 mg/m^2 every 2 weeks, based on the recommended 50% dose reduction for conventional VCR in subjects with impaired liver function. Grade 3 adverse events were seen in three (43%) patients. Nausea and constipation were common adverse events and were usually mild. Grade 1 neuropathy, presenting as numbness in fingers and toes, was seen in 43% of patients.[41]

Table 1 Clinically important drug interactions with vincristine

Drug	Effect on vincristine concentration	Mechanism of interaction
Aprepitant	Variable	CYP3A4 inhibition then induction
Azole antifungals	Increase	CYP3A inhibition
Nifedipine	Increase	CYP3A and P-glycoprotein inhibition
Cyclosporin A	Increase	CYP3A and P-glycoprotein inhibition
Erythromycin	Increase	CYP3A inhibition
HAART	Variable	CYP3A inhibition and induction
Corticosteroids	Decrease	CYP3A induction
Carbamazepine	Decrease	CYP3A4 induction
Phenytoin	Decrease	CYP3A induction

Notes: Reproduced with permission of Wiley and Sons. Moore A, Pinkerton R. Vincristine: can its therapeutic index be enhanced? *Pediatr Blood Cancer*. 2009;53(7):1180–1187.[22]

Abbreviations: CYP, cytochrome P450; HAART, highly-active antiretroviral therapy.

Drug–drug interactions

As VCR is usually given as combination chemotherapy in the treatment of ALL, it is important to be mindful of the potential adverse drug interactions. Particular considerations are the potential of the liposomal drug to change the PK of a coadministered free drug, and the potential for a free drug to affect the behavior of the liposomal carrier and encapsulated drug. The interactions between combination therapy with VSLI and mitoxantrone hydrochloride, idarubicin hydrochloride, daunorubicin hydrochloride, and doxorubicin hydrochloride have been assessed in vitro.[45] The addition of free daunorubicin was found to cause release of 26% of encapsulated VCR within 2 hours, followed by a 99% increase in uptake of daunorubicin into the liposomes.[45] The only agent studied in vivo in mouse models was idarubicin, which was not found to impact on the release of VCR from liposomes in the plasma compartment, in contrast to causing a rapid release of approximately 30% of encapsulated VCR in in vitro models.[45] Idarubicin was, however, found to have altered PK when administered shortly after VSLI injection, with increased free idarubicin concentrations at 15 and 60 minutes postadministration. Thus, it has been recommended that VSLI be administered at a time point when other free drug concentrations are low, to minimize drug–drug interactions.[45] VCR is known to undergo oxidization in the liver to one metabolite, M1, by the cytochrome P450 (CYP) group of enzymes – in particular, selective metabolism by CYP3A5. This may be clinically important due to the expression of CYP3A5 polymorphisms, with subsequent inter-racial differences in expression and potential effects on VCR efficacy and toxicity.[22] There are no specific interactions reported with the liposomal formulation of VCR, but other known interactions with free VCR would still apply to the use of VSLI, including drugs known to inhibit these CYP3A enzymes or P-glycoprotein and induce CYP3A enzymes (Table 1).[22]

Intrathecal administration

Inadvertent intrathecal administration of VCR is universally fatal.[46] It is expected that this catastrophic complication

Table 2 Currently open clinical trials of vincristine sulfate liposomal injection

Identifier	Title	Disease	Phase	Age
NCT01439347[49]	A Phase 3 Study to Evaluate Marqibo® in the Treatment of Subjects ≥60 Years Old With Newly Diagnosed ALL	Ph– ALL	III	≥60 years
NCT01319981[50]	Hyper-CVAD With Liposomal Vincristine in Acute Lymphoblastic Leukemia	ALL (Ph– and Ph+)	II	≥18 years
NCT00873093[51]	Bortezomib and Combination Chemotherapy in Treating Young Patients With Relapsed Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma	ALL and lymphoblastic lymphoma	II	1–31 years
NCT01222780[52]	To Evaluate the Safety, Activity and Pharmacokinetics of Marqibo in Children and Adolescents with Refractory Cancer	Multiple	I and II	2–21 years
NCT01478542[53]	OPTIMAL >60, Improvement of Therapy of Elderly Patients With CD20+ DLBCL Using Rituximab Optimized and Liposomal Vincristine	CD20+ B-non-Hodgkin's lymphoma	III	61–80 years
NCT01096368[54]	Maintenance Chemotherapy or Observation Following Induction Chemotherapy and Radiation Therapy in Treating Younger Patients With Newly Diagnosed Ependymoma	Ependymoma	III	1–21 years
NCT01055314[55]	Temozolomide, Cixutumumab, and Combination Chemotherapy in Treating Patients with Metastatic Rhabdomyosarcoma	Metastatic Rhabdomyosarcoma	Not specified	1 month to 49 years
NCT00506142[56]	Safety and Efficacy of Marqibo in Metastatic Malignant Uveal Melanoma	Metastatic melanoma	II	≥18 years

Abbreviations: ALL, acute lymphoblastic leukemia; CD, cluster of differentiation; CVAD, cyclophosphamide, vincristine, doxorubicin (adriamycin), dexamethasone; DLBCL, diffuse large B-cell lymphoma; Ph, Philadelphia chromosome; –, negative; +, positive.

would also apply to VSLI. Thus, standard precautions to reduce the risk of erroneous administration should remain a priority.

Pediatric experience

There are limited data on the use of VSLI in the pediatric setting, although early results from an ongoing trial on VSLI in children and adolescents are promising. In this single-center, Phase I dose-escalation study of VSLI in patients aged 2–18 years, six with ALL and three with solid tumors, patients received weekly VSLI for 4 weeks at doses of 1.75 mg/m^2 and 2.24 mg/m^2 with no dose capping.[47] One patient required dose de-escalation at the third VSLI dose due to neuropathy, and no patients were removed from the study due to neurotoxicity. Overall, the use of VSLI was demonstrated to be safe, with a similar toxicity profile in children and adults.[47]

Patient-focused perspectives

The ultimate goal of any new anticancer therapy is to improve response with reduced toxicity. The potential for improved efficacy with reduced peripheral and autonomic neurotoxicity would be a major advantage compared with free VCR. Although uncommon, free VCR-related peripheral neuropathy can be debilitating, and autonomic neuropathy can result in acute colonic pseudo-obstruction.[48]

Conclusion

There are currently eight open clinical trials of VSLI registered on ClinicalTrials.gov, three of which are for patients with ALL (Table 2). Importantly, a number of studies in ALL and other malignancies are evaluating VSLI with multiagent chemotherapy. Given the importance of VCR for both Ph– and Ph+ ALL, leukemia trials of VSLI are also now including Ph+ patients. Clinical experience to date suggests that VSLI is well tolerated at doses greater than those currently used for free VCR. Whether this translates to improved outcomes remains to be seen. For ALL, particularly pediatric ALL where outcomes are generally excellent and chemotherapy regimens are complex, reduction in VCR-related toxicity may be a more realistic aim for VSLI. Nonetheless, tolerable dose escalation of VCR may still contribute to improved clinical responses, particularly in high-risk patients.

Although the pursuit of molecularly targeted therapeutics for cancer remains critical, novel small molecules such as kinase inhibitors are rarely curative as single agents. Conventional cytotoxic chemotherapy will continue to form the backbone of anticancer treatment for the foreseeable future, so strategies to improve the therapeutic window of existing (and proven) anticancer drugs, such as encapsulation of VCR in liposomes, remain an important part of cancer drug discovery.

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