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Vincristine Sulfate Liposomes Injection (VSLI, Marqibo®): Results From a Phase I Study in Children, Adolescents, and Young Adults With Refractory Solid Tumors or Leukemias

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Abstract

Background.—Vincristine sulfate liposome injection (VSLI; Marqibo®) is an encapsulated preparation of standard vincristine in sphingomyelin/cholesterol liposomes. Clinical trials in adults have demonstrated safety, tolerability, and activity, leading to Food and Drug Administration (FDA) approval for adults with relapsed acute lymphoblastic leukemia (ALL). Pediatric experience with VSLI is limited.

Procedure.—This single center, phase I dose escalation study examined the safety, toxicity, maximum tolerated dose, and pharmacokinetics of VSLI administered weekly to pediatric patients age <21 years with relapsed or chemotherapy-refractory solid tumors or leukemia.

Results.—Twenty-one subjects were treated in total. Median age was 13.3 years (range 2–19). Fourteen subjects completed one 28-day cycle of therapy and five subjects completed more than one cycle. No subject experienced dose-limiting toxicity (DLT) at the first dose level (1.75 mg/m²/dose, dose range: 2–3.7 mg). At the second dose level (2.25 mg/m²/dose, dose range: 1.3–4.5 mg), one subject had transient dose-limiting grade 4 transaminase elevation, and this dose level was expanded with no additional DLT observed. The second dose level then opened to an expansion phase to evaluate activity in ALL. Clinical activity included minimal residual disease negative

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Authors contribution

N. N. S. wrote the paper, directly contributed to protocol enrollment and implementation of the study and patient care, collected and assembled data, including data analysis and interpretation, and is the current principal investigator of the trial. M.S.M. contributed to conception and design. D.E.C. and N.J. were involved with data analysis and interpretation. D.B., C.D., and K.R. all contributed to collection and assembly of data. B.C.W. contributed to conception and design, collection and assembly of data, and data analysis and interpretation. A.S.W. was the principal investigator of this trial and directly contributed to conception and design, study implementation, protocol enrollment, patient care, collection and assembly of data, and data analysis and interpretation. All authors contributed to the manuscript writing and final approval of the manuscript.

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complete remission in one subject with ALL and stable disease in nine subjects. Clearance of total vincristine was found to be approximately 100-fold lower in comparison to published data using standard vincristine.

Conclusions.—Children tolerate 2.25 mg/m²/dose of weekly VSLI (the adult FDA-approved dose) with evidence for clinical activity without dose-limiting neurotoxicity. Future plans include studying VSLI as substitution for standard vincristine with combination chemotherapy in children with ALL.

Keywords

acute lymphoblastic leukemia; Marqibo®; pediatric; phase I

INTRODUCTION

Vincristine sulfate is a highly active agent in pediatric cancers but is associated with acute and long-term peripheral neuropathy.[1] While chemotherapy dose intensification has improved outcomes in pediatric malignancies,[2–4] vincristine intensification leads to increased neuropathy.[5] A trial intensifying vincristine conducted through the Children's Oncology Group Trial AALL0433 was terminated early due to excessive peripheral neuropathy in the intensification arm, especially in older children.[6] To reduce the risk of severe neurotoxicity, individual doses of vincristine are capped based (e.g., a standard vincristine dose is 1.5 mg/m²/dose to a maximum of 2 mg/dose). This limitation is particularly relevant to adolescents and young adults with cancer whose outcomes are generally worse than younger patients.[7] In this group, risk-adjusted chemotherapy intensification has the potential to improve outcomes.[8,9]

Vincristine sulfate liposome injection (VSLI; Marqibo®) is composed of standard vincristine encapsulated in sphingomyelin/cholesterol liposomes. This formulation was designed to increase the therapeutic index of vincristine, prolonging the half-life and increasing preferential tissue penetration to sites of disease relative to normal tissues.[10–12] Notably, these properties obviate the need for dose capping, thus allowing vincristine dose intensification.

VSLI has been well studied in adults with relapsed or chemotherapy-refractory cancer, with promising results.[13–15] Results from a pivotal multicenter, singleagent phase II study of VSLI in adults with acute lymphoblastic leukemia (ALL) demonstrated a 20% complete response rate in heavily pretreated patients with relapsed/refractory disease, all of whom had prior vincristine exposure.[13] These results led to accelerated approval by the U.S. Food and Drug Administration (FDA) of VSLI at a dose of 2.25 mg/m²/dose given weekly for use in adults with relapsed ALL.[16,17] Combination chemotherapy trials in adults have demonstrated the safety and efficacy of utilizing VSLI in place of standard vincristine.[18] Only one prior study of VSLI has been performed in pediatrics, the results of which were not published and complete pharmacokinetic (PK) data were limited to two patients.[19]

This phase I dose escalation trial was conducted to evaluate the safety, toxicity, maximum tolerated dose (MTD), and PKs of weekly dosing of VSLI in children and adolescents with

relapsed and chemotherapy-refractory solid tumors or hematologic malignancies. Additional objectives were to define the tolerability and potential activity of VSLI in patients with ALL treated at the MTD.

PATIENTS AND METHODS

Patients

Pediatric patients (age 2–20 years) with relapsed or chemotherapy refractory malignancies with measurable or evaluable disease were eligible. Eligibility criteria required that subjects enroll a minimum of 7 days following chemotherapy and 30 days following investigational or monoclonal antibody therapy. Subjects with a prior history of stem cell transplantation were eligible in the absence of active graft-versus-host disease and without immunosuppressive therapy for at least 4 weeks. Other inclusion criteria included performance status of ≥ 50 , adequate liver function with bilirubin $< 2 \times$ the upper limit of normal and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $< 5 \times$ the upper limit of normal, and normal serum creatinine for age. A neutrophil count $> 1,000/\mu\text{L}$ and platelet count $> 50,000/\mu\text{L}$ were required unless due to marrow involvement by disease.

Subjects with preexisting grade 2 sensory or motor neuropathies, history of persistent grade 2 active neurologic disorders unrelated to chemotherapy, active central nervous system leukemia or lymphoma, or systemic uncontrolled infection were excluded. The use of azole-based antifungal agents was prohibited due to drug interactions. This protocol was reviewed and approved by the National Cancer Institute (NCI) institutional review board. Informed consent, or parental permission with child assent, was obtained in patients in accordance with institutional guidelines.

Study Design and Treatment

This was a single center, phase I dose escalation study sponsored by Spectrum Pharmaceuticals, Inc. (<http://www.clinicaltrials.gov/show/NCT01222780>). A rolling-six design was employed for subject accrual.[20] Subjects received once per week VSLI monotherapy based on an actual body surface area and without dose capping for a total of four doses per cycle. All subjects who received at least one dose of VSLI were evaluable for toxicity; however, subjects who did not complete at least one full cycle (four doses) for reasons other than dose-limiting toxicity (DLT) were not evaluable for determination of the MTD. Such patients were replaced until a cohort with at least three evaluable subjects was completed.

All VSLI doses were prepared and administered in accordance with the product prescribing information (<http://www.marqibo.com/>). The starting dose was $1.75 \text{ mg/m}^2/\text{dose}$ (80% of the adult MTD). Dose level 2 was $2.25 \text{ mg/m}^2/\text{dose}$. VSLI dosing was based on the vincristine component of the drug. VSLI was administered intravenously via peripheral or central venous access over 60 min on days 1, 8, 15, and 22 of a 28-day course in an outpatient or inpatient treatment setting. Subjects continued dosing for a full treatment cycle (four doses) unless there was evidence of disease progression or DLT. In the absence of DLT and with evidence clinical response, additional cycles of therapy were administered. Dose

modification was not allowed during the first treatment cycle. After the first cycle, delay in dosing up to 1 week was permitted to allow resolution of toxicity to pretreatment requirements. Dose deescalation was also allowed for subsequent cycles based on a prespecified algorithm if there was evidence of grade 2 sensory or motor peripheral neuropathy.

Dose-Limiting Toxicity

Toxicity was graded according to the NCI Common Toxicity Criteria for Adverse Events (Version 4.0). Nonhematologic DLT was defined as any grade 3–5 toxicity related to VSLI occurring during the first cycle, with exceptions for medically manageable grade 3 toxicities (e.g., low electrolyte levels). Hematologic DLT was defined by any grade 4 toxicity lasting greater than 5 days or for which transfusion support was required or by the failure to recover a neutrophil count to $1,000/\mu\text{l}$ or a baseline platelet count by day 35 of the treatment cycle. Grade 4 neutropenia lasting <1 week was not considered DLT. Subjects with abnormal blood counts (grade 1 through 4) at baseline due to marrow involvement were not evaluable for hematologic toxicity. Toxicity data from the first treatment cycle only were used in the MTD determination.

Pharmacokinetics

Detailed PKs were obtained on each subject as feasible, with all samples drawn from a line separate from that used for drug infusion. Samples were collected during cycle 1 before the start of the first infusion, 5 min postinfusion, and at 1, 3, 6, 10, 24, 48, 72, 96, 120, and 144 hr (predose #2 trough level). Following blood collection into ethylenediaminetetraacetic acid (EDTA) tubes, samples were placed on ice immediately and stored in a refrigerator until processing by separating plasma by centrifugation for 15 min at 10°C following validated procedures. A validated high performance liquid chromatography (HPLC) tandem mass spectrometry assay with a range of 40 ng/ml (lower limit of quantification) to 10,000 ng/ml was used to quantitate total (liposomal encapsulated, nonencapsulated, and protein bound) vincristine (see detailed method in Supplementary Text S1).

Vincristine concentration-time data were analyzed using noncompartmental methods. Peak vincristine concentration (C_{max}) and time to peak concentration were determined from each patient's concentration-time plot. Area under the concentration-time curve (AUC) to last measured time point after dose 1 was calculated with the linear trapezoidal method and extrapolated to infinity ($\text{AUC}_{0-\infty}$) by adding the last plasma concentration after dose 1 divided by the rate constant, which was derived from the slope of the natural log-transformed concentrations and times on the terminal elimination phase of the concentration-time curve. Half-life was calculated by dividing 0.693 by the terminal rate constant. Clearance was determined from $\text{dose}/\text{AUC}_{0-\infty}$. The relationship between clearance and age was evaluated by linear regression. Statistical analysis using Mann-Whitney tests was used to compare clearance and terminal half-life in patients who were younger than 13 (based on median age) to those who were 13 and above, and also used in comparing drug exposure to treatment response. All P -values were two-sided and level for statistical significance was set at <0.05 .

Evaluation of Clinical Activity

Standard response criteria were employed.[21–23] All subjects had baseline disease assessment within 14 days prior to the first dose of VSLI. In subjects with ALL, evaluation included cerebrospinal fluid (CSF) analysis, bone marrow aspirate/biopsy for morphology, flow cytometry, and monitoring of peripheral blasts when present. In subjects with solid tumors or extramedullary leukemia involvement, disease-specific imaging consisted of computed tomography and/or fludeoxyglucose-positron emission tomography. Postcycle evaluation was performed at day 28 ($\pm$ 3 days) of each cycle. Subjects who completed one full cycle or discontinued therapy early for disease progression were evaluable for response.

RESULTS

Patient, Disease, and Treatment Characteristics

From July 2011 through March 2014, a total of 22 subjects were enrolled, of which 21 subjects received at least one dose of VSLI. The median subject age was 13.3 years, with a range from 2 to 19 years. Eighteen subjects had relapsed ALL and one each had a diagnosis of Burkitt lymphoma, alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, and Ewing sarcoma. All subjects were heavily pretreated and had received a median of four prior regimens (range, 2–8), and all had previously received vincristine. Seven of 18 (39%) subjects with ALL had undergone a prior allogeneic hematopoietic stem cell transplant (Table I).

Fourteen subjects completed at least one cycle of therapy and five subjects received more than one cycle (median, 1; range, 0–3). One subject was enrolled but not treated due to interval development of ALL-related complications. One patient developed DLT at dose level 2. Six subjects did not complete a full cycle of VSLI and were removed from the study for reasons unrelated to VSLI toxicity. This included disease progression ($n = 3$), alternative therapy ($n = 2$), and severe viral respiratory infection ($n = 1$).

VSLI doses administered to subjects ranged from 1.3 to 4.5 mg/dose (median, 2.9 mg). Seventeen of 21 (81%) subjects received individual VSLI doses that exceeded the commonly employed 2 mg maximum for standard vincristine. The median cumulative dose was 10.4 mg (range, 3.4–30 mg) (Table II).

Toxicity

No subject experienced DLT at the first dose level (1.75 mg/m²/dose). At the second dose level (2.25 mg/m²/dose), one subject had grade 4 AST and ALT elevations after the first dose that met criteria for DLT and this dose level was expanded to a total of six evaluable subjects. Notably, this patient had prior history of recurrent grade 3 and 4 hepatic transaminase elevations related to multiple chemotherapy agents and also had developed hepatosplenomegaly and grade 3 hepatic transaminase elevation associated with disease progression immediately prior to starting therapy. No other subjects experienced DLT (Table III).

Most VSLI-related adverse events were reversible grade 1 and 2 in severity including transient hepatic transaminase elevations that resolved by the time of subsequent dose administration, paresthesia, low white blood cell count, neutropenia, and fatigue. Four subjects evaluable for hematologic toxicity developed grade 4 neutropenia that spontaneously and rapidly resolved. No subject was taken off study due to neurotoxicity. One subject met criteria for dose reduction with the third dose in cycle 2 (dose 6) due to paresthesia. He went on to complete six additional doses of VSLI at the lower dose without further complication. Fever was frequently observed within 24–48 hr of receiving the first dose ($n = 9$, 43%), and acetaminophen prophylaxis was used in these patients for subsequent dosing. Notably, pyrexia was the most common adverse event seen in the corresponding prior pediatric experience.[19]

The highest dose level tested was the adult MTD of 2.25 mg/m^2 . Although the MTD had not been exceeded at dose level 2, the decision was made to forego further dose escalation and to open the expansion cohort for subjects with ALL at dose level 2 in accordance with protocol allowances. This was based on the observed toxicity profile and clinical activity at dose level 2 ($2.25 \text{ mg/m}^2/\text{dose} \times 4$ weekly doses), which also represented the FDA-approved dose and schedule for adults, and the likelihood that the safety profile would be negatively impacted by further dose escalation and cumulative dosing. Notably, ongoing dosing of VSLI appeared to be associated with the development of peripheral neuropathy on this trial, consistent with results in adults with ALL where cumulative dose was correlated with earlier onset and higher grade neurotoxicity.[24] Specifically, two subjects who completed at least one cycle of therapy at the second dose level developed peripheral motor and sensory neuropathy. In one subject, this was a grade 2 event that would have invoked a treatment delay had therapy been continued, and in the other subject grade 2 peripheral motor and sensory neuropathy developed several weeks after the completion of one cycle. Notably, both of these subjects were teenagers, and higher rates of neurotoxicity have been observed in older children and adolescents with standard vincristine.[6]

Pharmacokinetics

PK parameters demonstrated wide interpatient variability (Tables II and IV). While an increase in the maximal VSLI concentration was observed with increasing dose, there was no increase in the median drug exposure with dose increase. There was also substantial variability in the terminal half-life and clearance (Figs. 1A and 1B). No relationship was seen between age and clearance (Fig. 1C) or total drug exposure. A nonstatistically significant trend was observed in the relationship between age and half-life (Fig. 1D). Specifically, the median half-life was shorter at 4.85 hr (range: 1.8–40.4 h, $n = 8$) in those who were younger than 13 years compared to a median half-life of 16.3 hr (range: 5.9–24.1 hr, $n = 11$) in those who were 13 and older ($P = 0.06$). Notably, in the lower age group, one patient had a remarkably long terminal half-life of 40.4 hr, which far exceeded that observed in any other subject. This subject also had the highest drug exposure ($\text{AUC}_{0-\infty} 77,429 \text{ ng/ml-hr}$). Interestingly, this subject had grade 4 hypertriglyceridemia prior to starting VSLI that was attributed to recent asparaginase therapy.[25] We hypothesized that the hypertriglyceridemia may have led to delayed clearance and increased exposure. The patient who developed DLT did not have increased drug exposure ($\text{AUC}_{0-\infty} 25,173 \text{ ng/ml-hr}$) in

comparison to other subjects. Figure 1E demonstrates the variable plasma concentration $\times$ time ($C \times T$) profiles for two patients treated at dose level 1. Individual plasma concentration-time profiles for 13 patients treated at the 2.25 mg/m² dose level are presented in the Supplementary Figure S1.

Clinical Activity

One subject with refractory ALL and posttransplant relapse attained a complete response that was shown to be minimal residual disease negative by flow cytometry after the second cycle, who notably also had the highest drug exposure (Fig. 2). Several subjects with ALL and peripheral blasts were noted to have a dramatic reduction in the absolute peripheral blast count after a single dose of VSLI (Fig. 2). One subject demonstrated hematologic improvement and achieved transfusion independence. Nine subjects had stable disease. Four subjects had progressive disease (Table II).

DISCUSSION

Dose intensification of chemotherapy has led to improved outcomes in pediatric cancer.[2–5] Intensification of standard vincristine, however, has been limited by neurotoxicity, and the maximum individual vincristine dose is usually capped at 2 mg/dose and the total number of weekly doses constrained. The pharmacologic and pharmacodynamic properties of VSLI would appear to support intensification of vincristine therapy in the treatment of high-risk pediatric malignancies. [17, 24] Our study provides the first experience administering VSLI with weekly dosing in children and adolescents following an intensive schedule that is frequently utilized in pediatric chemotherapy regimens. This phase I study enrolled heavily pretreated subjects with multiply relapsed and/or chemotherapy-refractory cancers, all of whom had prior vincristine exposure. Notably, VSLI was well tolerated despite weekly administration without dose capping, which allowed for significant dose intensification in comparison to standard vincristine. The median dose of VSLI administered was 2.9 mg (range, 1.9–4.5 mg) (Table II). Seventeen of 21 (81%) treated subjects received a VSLI dose that exceeded the 2 mg conventional dose limit set for standard vincristine. Though an MTD was not reached, based on the observed toxicity profile and the goal to avoid cumulative toxicity, further dose escalation was not pursued and the recommended phase II dose was defined as 2.25 mg/m²/dose given once every 7 days, which is the FDA-approved regimen for adults with ALL.

The PK profile of VSLI in pediatrics demonstrated wide interpatient variability, and no increase in drug exposure with increasing dose was observed in the small patient sample studied. The plasma concentration-time curves for VSLI were monoexponential for most patients (Fig. 1E), in contrast to vincristine, which typically exhibits triexponential curves. [26, 27] Our assay measured total vincristine (liposomal encapsulated, nonencapsulated, and protein bound) and thus could not differentiate or provide information about the proportion of vincristine that was encapsulated versus nonencapsulated. We also observed a trend toward an association between younger age and shorter half-life, (Fig. 1D) but without any difference in clearance. Interestingly, the patient (Subject #6) who achieved a complete response had the highest drug exposure as measured by maximum concentration, area under

the curve, and half-life (Table IV, Fig. 1E). The clearance of total vincristine in this patient was found to be at least 100-fold lower in comparison to reported PK data after administration of standard vincristine.[26–29]

A comparison of PK parameters of total vincristine in children to those in adults demonstrates greater variability and greater median drug exposure in children. At the 2.25 mg/m² dose level drug exposure in children (median 31,043 ng/ml-hr, range 11,856–63,964 ng/ml-hr) exceeded that in adults (median 13,680 ng/ml-hr, range 7,036–26,074 ng/ml-hr) by 2.3-fold.[17] The published adult data are not provided in detail, which limits the comparison. Notably, however, PK samples were processed using the same validated procedures, so variation in handling does not explain these differences. The sample size for both studies is small and future investigations in pediatric and adult patients will allow further characterization of potential differences in the PKs of total vincristine.

Comparative plasma and CSF PKs of vincristine compared to VSLI in our nonhuman primate model allowed for a direct comparison of vincristine and VSLI PKs and demonstrated that the clearance of vincristine (33.8 ml/min) exceeded that of VSLI (0.089 ml/min) by approximately 400-fold.[30] Additionally, no penetration into the CSF was observed for either preparation.[30]

Clinical activity was observed on this single agent trial. Most notably, one subject with multiply relapsed and chemotherapy refractory ALL who had relapsed after two prior allogeneic hematopoietic stem cell transplants attained a minimal residual disease negative complete response after two cycles of therapy. Additionally, two subjects had dramatic reductions in peripheral blasts with the first dose of VSLI. Two subjects with solid tumors had stable disease for two and three cycles of therapy.

The majority of patients did not continue therapy beyond one cycle. Thus, there was limited ability to assess for cumulative toxicity, specifically for neurotoxicity, which has been the main limiting factor with vincristine intensification. However, subjects did receive a median cumulative dose of 10.4 mg (range 3.4–30 mg). Ongoing studies in adults comparing vincristine to VSLI in randomized studies will be informative.

In conclusion, children and adolescents with relapsed/refractory cancer tolerate VSLI administered at 2.25 mg/m²/dose weekly x 4, which is also the MTD identified in adults, with a comparable toxicity profile and single-agent clinical activity. Based on tolerability and clinical activity, a pilot trial incorporating VSLI as substitution for standard vincristine with combination chemotherapy in patients with relapsed ALL is planned. The goal is to use VSLI with combination chemotherapy to allow for dose intensification with the aim to improve survival outcomes with reduced or comparable neurotoxicity in comparison to standard vincristine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Weiden PL, Wright SE. Vincristine neurotoxicity. *N Engl J Med* 1972;286:1369–1370.
2. Bowman WP, Larsen EL, Devidas M, Linda SB, Blach L, Carroll AJ, Carroll WL, Pullen DJ, Shuster J, Willman CL, Winick N, Camitta BM, Hunger SP, Borowitz MJ. Augmented therapy improves outcome for pediatric high risk acute lymphocytic leukemia: Results of Children's Oncology Group trial P9906. *Pediatr Blood Cancer* 2011;57:569–577. [PubMed: 21360654]
3. Matloub Y, Bostrom BC, Hunger SP, Stork LC, Angiolillo A, Sather H, La M, Gastier-Foster JM, Heerema NA, Sailer S, Buckley PJ, Thomson B, Cole C, Nachman JB, Reama G, Winick N, Carroll WL, Devidas M, Gaynon PS. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: A report from the Children's Oncology Group. *Blood* 2011;118:243–251. [PubMed: 21562038]
4. Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, Marcus K, Sailer S, Healey JH, Dormans JP, Weiss AR. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized ewing sarcoma: A report from the Children's Oncology Group. *J Clin Oncol* 2012;30:4148–4154. [PubMed: 23091096]
5. Nachman J, Sather HN, Gaynon PS, Lukens JN, Wolf L, Trigg ME. Augmented Berlin-Frankfurt-Munster therapy abrogates the adverse prognostic significance of slow early response to induction chemotherapy for children and adolescents with acute lymphoblastic leukemia and unfavorable presenting features: A report from the Children's Cancer Group. *J Clin Oncol* 1997;15:2222–2230. [PubMed: 9196134]
6. Lew G, Yanofsky R, Winick N, Rheingold S, Jorstad D, Lu X, Devidas M, Whitlock J, Hunger SP, Carroll WL. Intensive vincristine is not feasible in intermediate-risk relapse of childhood acute lymphoblastic leukemia (ALL): A report from Children's Oncology Group study AALL0433 (American Society of Pediatric Hematology/Oncology 25th Annual Meeting Abstract, #159). *Pediatr Blood Cancer* 2011;58:919.
7. Freyer DR, Felgenhauer J, Perentesis J. Children's Oncology Group's 2013 blueprint for research: Adolescent and young adult oncology. *Pediatr Blood Cancer* 2013;60:1055–1058. [PubMed: 23424167]
8. Pui CH, Pei D, Campana D, Bowman WP, Sandlund JT, Kaste SC, Ribeiro RC, Rubnitz JE, Coustan-Smith E, Jeha S, Cheng C, Metzger ML, Bhojwani D, Inaba H, Raimondi SC, Onciu M, Howard SC, Leung W, Downing JR, Evans WE, Relling MV. Improved prognosis for older adolescents with acute lymphoblastic leukemia. *J Clin Oncol* 2011;29:386–391. [PubMed: 21172890]
9. Ramphal R, Meyer R, Schacter B, Rogers P, Pinkerton R. Active therapy and models of care for adolescents and young adults with cancer. *Cancer* 2011;117:2316–2322. [PubMed: 21523752]
10. Webb MS, Harasym TO, Masin D, Bally MB, Mayer LD. Sphingomyelin-cholesterol liposomes significantly enhance the pharmacokinetic and therapeutic properties of vincristine in murine and human tumour models. *Br J Cancer* 1995;72:896–904. [PubMed: 7547237]
11. Webb MS, Logan P, Kanter PM, ST-Onge G, Gelmon K, Harasym T, Mayer LD, Bally MB. Preclinical pharmacology, toxicology and efficacy of sphingomyelin/cholesterol liposomal vincristine for therapeutic treatment of cancer. *Cancer Chemother Pharmacol* 1998;42:461–470. [PubMed: 9788572]
12. Krishna R, Webb MS, St Onge G, Mayer LD. Liposomal and nonliposomal drug pharmacokinetics after administration of liposome-encapsulated vincristine and their contribution to drug tissue distribution properties. *J Pharmacol Exp Ther* 2001;298:1206–1212. [PubMed: 11504822]

13. O'Brien S, Schiller G, Lister J, Damon L, Goldberg S, Aulitzky W, Ben-Yehuda D, Stock W, Coutre S, Douer D, Heffner LT, Larson M, Seiter K, Smith S, Assouline S, Kuriakose P, Maness L, Nagler A, Rowe J, Schaich M, Shpilberg O, Yee K, Schmeider G, Silverman JA, Thomas D, Deitcher SR, Kantarjian H. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult philadelphia chromosome-negative acute lymphoblastic leukemia. *J Clin Oncol* 2013;31:676–683. [PubMed: 23169518]
14. Rodriguez MA, Pytlik R, Kozak T, Chhanabhai M, Gascoyne R, Lu B, Deitcher SR, Winter JN. Vincristine sulfate liposomes injection (marqibo) in heavily pretreated patients with refractory aggressive non-Hodgkin lymphoma: Report of the pivotal phase 2 study. *Cancer* 2009;115:3475–3482. [PubMed: 19536896]
15. Thomas DA, Kantarjian HM, Stock W, Heffner LT, Faderi S, Garcia-Manero G, Ferrajoli A, Wierda W, Pierce S, Lu B, Deitcher SR, O'Brien S. Phase 1 multicenter study of vincristine sulfate liposomes injection and dexamethasone in adults with relapsed or refractory acute lymphoblastic leukemia. *Cancer* 2009;115:5490–5498. [PubMed: 19708032]
16. U.S. Food and Drug Administration, FDA news release, <http://www.Fda.Gov/newsevents/newsroom/pressannouncements/ucm315027.Htm>. Accessed August 9, 2012.
17. Silverman JA, Deitcher SR. Marqibo® (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemother Pharmacol* 2013;71:555–564. [PubMed: 23212117]
18. Hagemester F, Rodriguez MA, Deitcher SR, Younes A, Fayad L, Goy A, Dang NH, Forman A, McLaughlin P, Medeiros LJ, Pro B, Romaguera J, Samaniego F, Silverman JA, Sarris A, Cabanillas F. Long term results of a phase 2 study of vincristine sulfate liposome injection (Marqibo®) substituted for non-liposomal vincristine in cyclophosphamide, doxorubicin, vincristine, prednisone with or without rituximab for patients with untreated aggressive non-Hodgkin lymphomas. *Br J Haematol* 2013;162:631–638. [PubMed: 23802738]
19. Herzog CE, Russo ML, Kuttlesch J. Phase II study of sphingosomal vincristine (SV), in pediatric malignancies (American Society of Pediatric Hematology/Oncology 18th Annual Meeting Abstract, #393). *Pediatr Blood Cancer* 2005;44:540.
20. Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. Shortening the timeline of pediatric phase I trials: The rolling six design. *J Clin Oncol* 2008;26:190–195. [PubMed: 18182661]
21. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25:579–586. [PubMed: 17242396]
22. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, Schiffer CA, Doehner H, Tallman MS, Lister TA, Lo-Coco R, Willemze R, Biondi A, Hiddemann W, Larson RA, Lowenberg B, Sanz MA, Head DR, Ohno R, Bloomfield CD. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol* 2003;21:4642–4649. [PubMed: 14673054]
23. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubenstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247. [PubMed: 19097774]
24. Silverman JA, Reynolds L, Deitcher SR. Pharmacokinetics and pharmacodynamics of vincristine sulfate liposome injection (VSLI) in adults with acute lymphoblastic leukemia. *J Clin Pharmacol* 2013;53:1139–1145. [PubMed: 23907766]
25. Parsons SK, Skapek SX, Neufeld EJ, Kuhlman C, Young ML, Donnelly M, Brunzell JD, Otvos JD, Sallan SE, Rifai N. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. *Blood* 1997;89:1886–1895. [PubMed: 9058708]
26. Sethi VS, Kimball JC. Pharmacokinetics of vincristine sulfate in children. *Cancer Chemother Pharmacol* 1981;6:111–115. [PubMed: 7307229]
27. Sethi VS, Jackson DV Jr., White DR, Richards F, Stuart JJ, Muss HB, Cooper MR, Spurr CL. Pharmacokinetics of vincristine sulfate in adult cancer patients. *Cancer Res* 1981;41:3551–3555. [PubMed: 7260915]

28. Crom WR, de Graaf SS, Synold T, Uges DR, Bloemhof H, Rivera G, Christensen ML, Mahmoud H, Evans WE. Pharmacokinetics of vincristine in children and adolescents with acute lymphocytic leukemia. *J Pediatr* 1994;125:642–649. [PubMed: 7931891]
29. Groninger E, Meeuwsen-de Boer T, Koopmans P, Uges D, Sluiter W, Veerman A, Kamps W, de Graaf S. Vincristine pharmacokinetics and response to vincristine monotherapy in an up-front window study of the Dutch childhood leukaemia study group (DCLSG). *Eur J Cancer* 2005;41:98–103. [PubMed: 15617994]
30. Shah NN, Cole DE, Lester-McCully CM, Wayne AS, Warren KE, Widemann BC. Plasma and cerebrospinal fluid pharmacokinetics of vincristine and vincristine sulfate liposomes injection (VSLI, Marqibo®) after intravenous administration in non-human primates. *Invest New Drugs* 2016;34(1):61–65. [PubMed: 26661090]

Fig. 1. Pharmacokinetics. Relationship of patient age to vincristine clearance (**A**) and terminal half-life (**B**). Comparison of clearance (**C**) and terminal half-life (**D**) between those subjects less than 13 years versus those 13 years and older. Example of representative plasma concentration-time curves, demonstrating variability in vincristine exposure in two patients treated at dose level 1 ($1.75 \text{ mg/m}^2/\text{dose}$) (**E**).

Fig. 2.

Clinical activity. Twelve-year-old male with refractory ALL and posttransplant relapse attained a minimal residual disease negative complete response after two cycles (**A**). Rapid reduction of absolute peripheral blast count after single dose of VSLI in two subjects with chemotherapy-refractory ALL (**B**) Subject 13: 5-year-old female (B1); subject 10: 5-year-old male (B2).

TABLE I.

Patient Characteristics

	Median	Range
Characteristics of all subjects (n = 22)		
Age	13.5 years	2–19 years
Male:Female	14:8	-
Performance status	90%	60–100%
Acute lymphoblastic leukemia	18	
Burkitt lymphoma	1	
Solid tumors ^a	3	
Prior regimens	4	
Prior vincristine exposure	22	
Characteristics of subjects with ALL (n = 18)		
White blood cell count	2,055/ μ l	80–38,660/ μ l
Peripheral blood blasts	23%	0–97%
Bone marrow blasts	83%	1–98%
Prior allogeneic hematopoietic stem cell transplant	7	
Precursor T-cell phenotype ^b	2	

^aEwing sarcoma, desmoplastic small round cell tumor, alveolar rhabdomyosarcoma

^bRemaining subjects had precursor B-cell phenotype

TABLE II.

Maximum Dose, Best Response, and Pharmacokinetic Results per Individual Subject

Patient no.	Age/sex	Diagnosis	Dose level	Dose (mg)	No. of doses received	No. of cycles received	Cumulative dose (mg)	DLT (Y/N)	AUQ _{0-∞} (ng/ml·hr)	C _{max} (ng/ml)	T _{1/2} (hr)	Best response
1	18.9/F	ALL	1	3.7	2	1 ^a	7.4	N	8,950	845	6.1	NE
2	15.2/M	ALL	1	2.5	4	1	10.0	N	61,890	1,870	10.2	SD
3	17.6/M	Solid	1	2.9 ^b	12	3	30.0	N	45,851	1,280	19.6	SD
4	11.6/M	ALL	1	2.5	2	1 ^a	4.9	N	6,586	1,690	1.8	NE
5	13.3/M	Solid	1	2.3	4	1	9.1	N	27,250	1,040	6.7	PD
6	12.6/M	ALL	1	2	12	3	24.0	N	77,429	2,120	40.4	CR
Median for dose level 1 Range												
7	2.3/F	Solid	2	1.3	8	2	10.4	N	36,551 6,586–77,429	1,485 845–2,120	8.5 1.8–40.4	SD
8	14.0/M	ALL	2	3.4	1	1 ^a	3.4	Y ^c	37,603	3,620	13.5	NE
9	14.1/M	ALL	2	4.1	4	1	16.4	N	44,088	2,450	19.3	PD
10	5.5/M	ALL	2	1.9	4	1	7.6	N	11,856	1,450	2.52	SD
11	15.5/M	BL	2	3	2	1 ^a	6.0	N	31,043	1,360	19.6	PD
12	19.8/M	ALL	2	N/A	0	0		N/A	N/A	N/A	N/A	Not treated ^d
13	5.5/F	ALL	2	2.1	3	1 ^a	6.3	N	30,653	2,150	9.1	NE
14	16.5/F	ALL	2	3.8	4	1	15.2	N	23,637	956	16.3	SD
15	16.1/M	ALL	2	4.3	2	1 ^a	8.6	N	63,964	1,650	22.5	NE
16	17.2/M	ALL	2	4.5	4	1	18	N	29,834	1,680	6.0	SD
17	10.2/M	ALL	2	2.5	9	3 ^a	22.5	N	36,958	2,650	6.2	HI
18	9.3/M	ALL	2	2.9	4	1	11.6	N	18,126	2,410	3.4	SD
19	16.0/F	ALL	2	3.3	4	1	13.2	N	39,559	2,430	24.1	PD
20	2.8/F	ALL	2	1.4	8	2	11.2	N	34,849	3,400	3.5	SD
21	6.6/F	ALL	2	1.9	2	1 ^a	3.8	N	-	-	-	PD
22	11.3/F	ALL	2	3.4	5	2 ^a	17	N	-	-	-	SD

Patient no.	Age/sex	Diagnosis	Dose level	Dose (mg)	No. of doses received	No. of cycles received	Cumulative dose (mg)	DLT (Y/N)	AUC _{0-∞} (ng/ml·hr)	C _{max} (ng/ml)	T _{1/2} (hr)	Best response
Median for dose level 2												
Range												
									31,043	2,150	10.7	
									11,856–63,964	956–3,620	3.4–24.1	

^aThe final cycle was not completed

^bsubject received six doses at 1.75 mg/m²/dose (2.9 mg) and then had a dose reduction due to paresthesias to 1.25 mg/m²/dose (2.1 mg) for the remaining six doses.

^cDLT: grade 4 hepatic transaminase elevation (both alanine aminotransferase and aspartate aminotransferase);

^denrolled but developed neutropenic typhilitis immediately prior to starting protocol therapy and was taken-off treatment for intercurrent illness. AUC(0–∞), Area under the concentration-time curve extrapolated to infinity; C_{max}, maximum (peak) concentration; T_{1/2}, elimination half-life. ALL, acute lymphoblastic leukemia; solid tumors: Subject 3, Ewing Sarcoma; Subject 5, desmoplastic small round cell tumor; Subject 7, alveolar rhabdomyosarcoma; BL, Burkitt's lymphoma; NE, not evaluable; SD, stable disease; PD, progressive disease; HI, hematologic improvement; CR, complete remission.

TABLE III.
Adverse Events During the First Treatment Cycle Possibly, Probably, or Definitely Related to VSLI

	Number of patients with toxicity grade by dose level (Highest grade/patient)									
	Dose level 1 1.75 mg/m ² /dose (n = 6)					Dose level 2 2.25 mg/m ² /dose (n = 15)				
	1	2	3	4		1	2	3	4	
<i>CTCAE v4 grade</i>										
<i>Blood and lymphatic system disorders</i>										
Anemia		1					1	1		
Lymphocyte count decreased		1	1							
Neutrophil count decreased		1	1	1				1	3	
White blood cell count decreased	1	1	1			1		2	4	
Platelet count decreased		1				1	2			
Febrile neutropenia								6		
PTT prolonged							1			
INR increased						1				
<i>Cardiac disorders</i>										
Sinus tachycardia	1					1				
Pericardial effusion							1			
<i>Gastrointestinal disorders</i>										
Abdominal distension						1				
Abdominal pain	2					5	1			
Anorexia	1					2	1			
Constipation						3	1			
Diarrhea						2				
Nausea	1					7				
Rectal hemorrhage						1				
Vomiting	1					3	1			
<i>Hepatobiliary disorders</i>										
ALT increased	1		2			1	3	4	1 ^a	
AST increased	3		2			3	2	6	1 ^a	
Bilirubin increased						2				

Number of patients with toxicity grade by dose level(Highest grade/patient)		
	Dose level 1 1.75 mg/m ² /dose (n = 6)	Dose level 2 2.25 mg/m ² /dose (n = 15)
<i>Nervous system disorders</i>		
Dizziness		1
Dyesthesia	1	
Gait disturbance	1	2
Headache		2
Muscle weakness		1
Myalgia	2	1
Nystagmus		1
Paresthesia	1	4
Peripheral motor neuropathy		1
Peripheral sensory neuropathy		1
Somnolence		1
Tremor		1
<i>General disorders</i>		
Back pain	1	1
Bone pain	1	2
Dry mouth		1
Fatigue	2	5
Fever	1	1
Sore throat		1
Oral pain		1
Stomach pain		1
Toothache		1
Pain (generalized)	1	1
Pain (extremity)	1	
Arthralgia		1
<i>Metabolism and nutrition disorders</i>		
CPK increased		2
Cholesterol high	1	1

Number of patients with toxicity grade by dose level(Highest grade/patient)		
	Dose level 1 1.75 mg/m ² /dose (n = 6)	Dose level 2 2.25 mg/m ² /dose (n = 15)
Hypercalcemia		1
Hypnatremia		1
Hypertiglyceridemia	1	3
Hyperuricemia		2
Hypoalbuminemia		1
Hypokalemia		1
Hypomagnesemia	1	4
Hypophosphatemia		1
Bicarbonate, low		1
<i>Renal and urinary disorders</i>		
Proteinuria		2
<i>Psychiatric disorders</i>		
Agitation		1
Insomnia		1
<i>Skin and subcutaneous tissue disorders</i>		
Alopecia	1	

^aDose-limiting toxicity.

^bPTT, activated partial thromboplastin time; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.
AST, aspartate aminotransferase; CPK, creatine phosphokinase

TABLE IV.

Summary of Pharmacokinetic Parameters

Dose level	No.	C _{max} (ng/ml)	AUC _(0-last) (ng/ml·hr)	AUC _(0-∞) (ng/ml·hr)	T _{max} (hr)	T _{1/2} (hr)	CL (ml/min/m ²)
1 (1.75 mg/m ²)	6	Median	34,651	36,551	1.5	8.5	0.855
		Range	845–2,120	6,426–74,224	1.0–2.02	1.8–40.4	0.43–4.52
2 (2.25 mg/m ²)	13	Median	29,919	31,043	1.12	10.7	1.2
		Range	956–3,620	11,793–62,441	1.0–2.08	3.4–24.1	0.58–3.19

C_{max}, maximum (peak) concentration; AUC_(0-last), area under the concentration-time curve to last measured time point; AUC_(0-∞), AUC extrapolated to infinity; T_{max}, time after the administration of a drug when the maximum plasma concentration is reached; T_{1/2}, elimination half-life; CL, clearance.