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Phase 1 Multicenter Study of Vincristine Sulfate Liposomes Injection and Dexamethasone in Adults With Relapsed or Refractory Acute Lymphoblastic Leukemia

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Abstract

BACKGROUND—Dose intensification of chemotherapy has improved outcome for younger adults with de novo acute lymphoblastic leukemia (ALL). Novel formulations of standard chemotherapy agents may further reduce the incidence of disease recurrence after frontline chemotherapy. Vincristine (VCR) sulfate liposomes injection (VSLI) is a sphingomyelin/cholesterol nanoparticle encapsulated VCR formulation that improves the pharmacokinetic profile of VCR without augmenting neurotoxicity.

METHODS—A phase 1 trial of weekly, intravenous VSLI at 1.5 mg/m², 1.825 mg/m², 2.0 mg/m², 2.25 mg/m², or 2.4 mg/m² was conducted to determine the maximum tolerated dose (MTD) using a standard, 3 + 3 dose-escalation design. Dexamethasone (40 mg) was given on Days 1 through 4 and on Days 11 through 14 of each 4-week cycle.

RESULTS—Thirty-six adults with relapsed/refractory ALL, all previously treated with conventional VCR, received at least 1 dose of VSLI. The MTD of VSLI was 2.25 mg/m² based on dose-limiting toxicities of grade 3 motor neuropathy, grade 4 seizure, and grade 4 hepatotoxicity in 1 patient each at the 2.4 mg/m² dose level. The most common toxicities attributed to VSLI included peripheral neuropathy (55%) and constipation (53%). A complete response (CR) was achieved in 7 of 36 patients (19%) based on an intent-to-treat analysis; the CR rate was 29% for

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Biao Lu and Steven R. Deitcher are employed by Hana Biosciences.

the 14 patients who underwent therapy as their first salvage attempt. Four of 7 patients who achieved a CR underwent subsequent allogeneic stem cell transplantation in remission.

CONCLUSIONS—In this study, VSLI plus dexamethasone appeared to be an effective salvage therapy option for relapsed/refractory ALL. A phase 2, international, multicenter clinical trial assessing the efficacy of single-agent VSLI as second salvage therapy for patients with previously treated ALL is underway.

Keywords

acute lymphoblastic leukemia; liposome; salvage therapy; vincristine

Significant improvements in outcome are being achieved in younger adults with de novo acute lymphoblastic leukemia (ALL) with the use of dose-intensive treatment programs modeled after pediatric regimens; long-term event-free survival (EFS) rates range from 60% to 70% compared with 30% to 40% after conventional adult chemotherapy.¹ This is attributed in part to higher dose intensity (and cumulative dose) of the anthracycline, vincristine (VCR), corticosteroids, and asparaginase components.

Novel formulations of standard chemotherapy agents that improve drug delivery without additional toxicity also may reduce the incidence of disease recurrence after frontline chemotherapy. The vinca alkaloid VCR has significant activity against aggressive non-Hodgkin lymphoma (NHL) subtypes and ALL, and it remains an integral component of chemotherapy regimens for these disease entities. VCR induces cell cycle-specific cytotoxicity by binding to tubulin during active mitosis, resulting in microtubule depolymerization and metaphase arrest.^{2,3} This, in turn, leads to apoptosis. In human leukemia cell lines, the degree of VCR-induced apoptosis in vitro increased proportionally with higher drug concentrations and longer duration of exposure. After intravenous administration, conventional VCR undergoes rapid cellular uptake and extensive tissue binding, resulting in a half-life on the order of minutes with low levels of free VCR in the plasma.⁴⁻⁶ Furthermore, the dose intensity and delivery of conventional VCR is limited by the significant peripheral and central nervous system (CNS) neurotoxicity, which ensues at doses higher than 1.4 mg/m² or at a “capped” dose of 2 mg.⁷⁻⁹

VCR sulfate liposomes injection (VSLI) (Marqibo; developed by Inex Pharmaceuticals Corporation, Burnaby, British Columbia, Canada and Enzon Pharmaceuticals Incorporated, Bridgewater, NJ) is a novel nanoparticle formulation of VCR encapsulated in the aqueous core of sphingomyelin and cholesterol liposomes called Optisomes. The encapsulation of VCR prolongs the circulation of active drug and passively targets drug to tissues with fenestrated vasculature (eg, bone marrow, lymph nodes, spleen, liver, and solid tumors), thereafter leading to first-order release kinetics with deposition of drug over several days.¹⁰⁻¹² VSLI has demonstrated significantly greater antitumor activity in vitro and in vivo in animal models compared with conventional VCR at equivalent (mg/kg) doses, and was more likely to be curative in murine systems against L1210 or P388 leukemia cell lines.¹³⁻¹⁶

A phase 1 clinical trial of single-agent VSLI was initially conducted in patients who had previously treated solid tumors. VSLI was dose escalated from 0.5 mg/m² to 2.8 mg/m² every 3 weeks.¹⁷ Dose-limiting toxicities (DLTs) were observed at the 2.8 mg/m² dose level and included myalgias, peripheral neuropathy, and constipation. It was determined that the maximum tolerated dose (MTD) was 2.4 mg/m², although toxicity profiles were similar at the 2 mg/m² and 2.4 mg/m² dose levels. The most frequent grade 3 and 4 toxicities observed over all dose levels were constipation (12%), fatigue (8%), alopecia (8%), and anemia (8%).

Next, a pivotal phase 2 study of VSLI was conducted among patients with recurrent, aggressive NHL using a dosing schema of 2 mg/m² every other week.¹⁸ After tolerability was established, the trial was extended to patients with relapsed or refractory ALL. Sixteen heavily pretreated, refractory patients (including 50% with Philadelphia chromosome [Ph]-positive ALL in the preimatinib era) received therapy with single-agent VSLI.¹⁹ The overall response rate in that group was 15%: There were 2 responders (1 complete remission [CR], 1 partial response [PR]), 4 patients had transient bone marrow cytoreduction. Neurotoxicity was minimal, but dosing was limited. To further optimize dose intensity and to discern the tolerance of multiple doses in the salvage setting, a multicenter phase 1 clinical trial of weekly dose-escalated VSLI was designed²⁰ in which patients received VSLI concurrently with pulse dexamethasone to facilitate multiple dosing.

MATERIALS AND METHODS

Eligibility Criteria

Patients who had previously treated ALL, including the lymphoblastic lymphoma and Burkitt leukemia/lymphoma (BLL) subtypes, were eligible if they had an Eastern Cooperative Oncology Group performance status ≤ 3, if they had total bilirubin and creatinine levels ≤ 2 times the upper limit of normal, and if serious active infections were controlled. At least 21 days must have elapsed since the previous antileukemia therapy except in patients who had rapidly progressive disease if they had recovered from previous toxicity. Previous stem cell transplantation (SCT) was allowed as long as the other eligibility criteria were met. Patients could not have known CNS disease that required active intrathecal (IT) chemotherapy or craniospinal radiation therapy, although asymptomatic, controlled CNS disease was allowed. Patients were also excluded on the basis of other neurologic criteria, including a history of grade 3/4 sensory or motor neuropathy with previous chemotherapy, persistent grade ≥ 2 active neuropathy, or active neurologic disorders unrelated to chemotherapy (eg, familial neurologic disorders or acquired demyelinating disorders). Pregnant women were not eligible. The protocol was reviewed by the institutional review boards of the respective institutions. Informed consent was obtained from patients in accordance with institutional guidelines and the Declaration of Helsinki.

Therapy

VSLI with a final VCR concentration of 0.16 mg/mL was reconstituted from a single-use, 3-vial kit (Almac, Durham, NC) and administered within 12 hours of preparation. VSLI was administered on a weekly basis as an intravenous infusion (either peripherally or through a central venous catheter) over 60 minutes at a dose of 1.5 mg/m², 1.825 mg/m², 2 mg/m²,

2.25 mg/m², or 2.4 mg/m² (no dose capping) concurrently with dexamethasone 40 mg intravenously or orally on Days 1 through 4 and Days 11 through 14 of each 4-week cycle. Therapy was continued thereafter in the absence of DLTs or disease progression for up to 12 cycles of therapy. Prophylactic therapy with stool softeners was strongly encouraged. The use of neurotropic agents, such as gabapentin and/or amitriptyline, was permitted for the management of peripheral neuropathy. Dose reductions and/or dose delays of the VSLI were implemented with subsequent cycles of therapy as indicated for persistent grade 2 or 3 VSLI-related nonhematologic toxicities (eg, peripheral neuropathy or constipation). Dose modifications were not required for medically manageable grade 3 toxicities (eg, fever without infection or emesis). If a grade 4 VSLI-related nonhematologic toxicity other than hyperglycemia was encountered (exclusive of expected toxicities, such as sepsis or other events related to underlying disease), then therapy was permanently discontinued. Hyperglycemia of any grade and other toxicities related to the dexamethasone were managed according to standard practice without dose modifications of the VSLI.

Assessments

Pretreatment evaluations included a history and physical examination with neurologic assessment; complete blood count with differential; chemistry profile, including hepatic and renal function tests; pregnancy test for women of childbearing potential; bone marrow aspiration; and radiographs of involved sites if the patient had known extra-medullary disease. Laboratory parameters and neurologic examinations were repeated at least weekly during the first cycle of therapy before each dose of VSLI. Bone marrow aspirations were obtained on Days 14 and 28 of the first cycle of therapy and as warranted thereafter to assess disease status. Abnormal radiographs of involved sites were repeated at the end of the first cycle to assess response.

Supportive Care

Appropriate transfusion support was provided with packed erythrocytes given for symptomatic and/or severe anemia, and platelets (PLTs) were given for thrombocytopenia according to institutional guidelines. All blood products were irradiated as feasible. Prophylactic antibiotics were encouraged during periods of neutropenia, including antibacterial agents (eg, quinolones), triazole antifungal agents (such as fluconazole, itraconazole, or voriconazole), and antiviral agents, such as acyclovir or valacyclovir. Filgastrim was not administered routinely but was permitted in patients who had infections associated with neutropenia.

Response Criteria

A CR included normocellular or hypercellular bone marrow with <5% blasts, a granulocyte count (absolute neutrophil count [ANC]) $1 \times 10^9/L$, and a PLT count $100 \times 10^9/L$. Resolution of extramedullary disease was required for CR. A PR was defined as normalization of the peripheral blood, similar to a CR with residual bone marrow blasts from 6% to 25%. Hematologic improvements (HIs) in cytopenias and/or bone marrow disease compared with pretreatment parameters also were categorized as measures of clinical benefit: improvements in 1) ANC by 50% and to $>1 \times 10^9/L$ (HI-ANC) if it was below that level, 2) hemoglobin by 2 g/dL if <10 g/dL or a decrease in transfusion

requirements by 50% (HI-HGB), 3) PLTs by 50% and to $50 \times 10^9/L$ if it was below that level or the achievement of transfusion-independence (HI-PLT), and 4) a reduction in bone marrow blasts to 5% (HI-BM). Patients who failed to meet any of these criteria or who had evidence of disease progression were considered nonresponders.

Statistical Analysis

The primary objective of this study was to determine the MTD of 4 weekly doses of VSLI administered concurrently with pulse dexamethasone (1 cycle). All patients who received at least 1 dose of VSLI were evaluable for toxicity; however, patients who did not complete 1 full cycle for reasons other than DLT were not evaluable for the MTD. Such patients were replaced until the cohort was completed. A traditional 3 + 3 phase 1 design was used to determine the feasibility of dose escalation. Once the MTD was established, up to 10 additional patients could be enrolled at that dose level to better characterize the toxicity profile. Secondary objectives of the study included assessments of efficacy as measured by the proportion of patients who achieved a CR or a PR in an intent-to-treat analysis. Response rates were reported with a 2-sided confidence interval (CI) using the exact method.²¹ Toxicity was assessed according to the National Cancer Institute Expanded Common Toxicity Criteria (version 3; National Cancer Institute, Bethesda, Md). Differences in response rates or pretreatment characteristics among subgroups were analyzed using the chi-square test or the Fischer exact test.²¹

RESULTS

Study Group

Between August 2002 and July 2006, 36 adults with previously treated recurrent or refractory ALL or BLL were enrolled (Table 1). The median age of the group was 32 years; 3 patients (8%) were aged 60 years, and 67% of patients were men. Three patients had extramedullary disease (peripheral lymphadenopathy, mediastinal mass, and intraabdominal adenopathy), and none had known CNS disease at the time of enrollment. The median first CR duration was 12 months (range, 2-83 months). Seven patients (19%) were refractory to initial induction chemotherapy. Six patients (17%) had undergone allogeneic SCT as consolidation therapy (n = 5) or salvage therapy (n = 1). All patients had previously received conventional VCR. One patient with Ph-positive ALL also had failed tyrosine kinase inhibitor-based therapy. The median time from initial diagnosis to therapy with VSLI and dexamethasone was 16 months (range, 3-102 months). VSLI-based therapy was the first salvage attempt in 14 patients (39%), the second salvage attempt in 14 patients (39%), and the third or greater salvage attempt in 8 patients (22%).

Delivery of Therapy and Toxicity

Of the entire cohort of patients that received VSLI and dexamethasone, 27 patients (75%) completed the first cycle (4 weekly doses of VSLI). Of the 25 patients who were enrolled before the MTD was determined, 5 patients (20%) had discontinued therapy early for reasons of toxicity (n = 2), progressive disease (n = 2), or patient request (n = 1). The latter 3 patients were replaced according to protocol design at the 1.5 mg/m² (n = 2) and 2.25 mg/m² (n = 1) dose levels.

The most frequently occurring toxicities, irrespective of grade, causality, VSLI dose level, or number of VSLI doses, included constipation (67%), fatigue (61%), peripheral neuropathy (55%), anemia (50%), and pyrexia (50%). Table 2 details all grade 3 and 4 toxicities (except for infections) that were attributed to therapy with VSLI and dexamethasone in addition to grade 1 and 2 toxicities that occurred at a frequency of 5%. The overall incidence of treatment-related peripheral neuropathy (55%) was similar across the treatment cohorts despite dose escalation of VSLI; however, the incidence of constipation increased (36% at 3 dose levels between 1.5 mg/m² and 2 mg/m² vs 60% at 2 dose levels between 2.25 mg/m² and 2.4 mg/m²). Grade 3 and 4 clinically relevant toxicity was not observed until the 2.25 mg/m² dose level was reached (Table 2). Three DLTs with at least possible or probable attribution to VSLI were observed at the 2.4 mg/m² dose level in 1 patient each, and included grade 3 motor neuropathy (probable), grade 4 seizure in the setting of intracranial hemorrhage (possible), and grade 4 hepatotoxicity (elevations in hepatic transaminase levels with the inability to exclude a possible drug-drug interaction with fluconazole). Grade 4 hyperglycemia also was observed in the patient with hepatotoxicity and was attributed to the dexamethasone. The MTD was established at 2.25 mg/m². An additional 11 patients (1 who was replaced because of early discontinuation) subsequently were enrolled at this dose level to better clarify the toxicity profile.

Febrile neutropenia (attributed to VSLI in 4 patients) occurred in 14 patients (39%) overall, and bacteremia was the etiology in 7 of those episodes (50%). Three younger patients (ages 24-31 years) died of infections during Cycle 1 of VSLI and dexamethasone, including 1 patient who died on Day 15 from *Aspergillus* pneumonia, 1 patient who died on Day 18 from presumed septicemia, and 1 patient who died on Day 18 from *Escherichia coli* septicemia.

Three of 14 patients (21%) who continued VSLI and dexamethasone beyond the first cycle underwent dose reductions of VSLI (to the next lower dose level) for reasons of grade 2/3 constipation (n = 2) or peripheral neuropathy (n = 1). The median number of VSLI doses administered overall was 4 (range, 2-11 VSLI doses). The median body surface area (BSA) for the group was 2.1 m² (range, 1.5-2.8 m²). The median calculated dose of VSLI was 4.17 mg (range, 2.9-5.7 mg), which represented an average increase in VCR dose of 52% (range, 31%-65% increase) compared with conventional administration. The median cumulative dose/BSA of VSLI was 9 mg/m² (range, 4.5-19.7 mg/m²), and the median cumulative dose was 19.2 mg (range, 10.2-38.1 mg).

Concurrent Therapy

Five patients received IT chemotherapy during the course of study participation. One patient developed CNS disease after 2 doses of VSLI and was treated with standard doses of alternating IT chemotherapy (cytarabine with methotrexate). The remaining 4 patients underwent diagnostic lumbar punctures concurrently with IT cytarabine to evaluate headaches (not attributed to VSLI), and 2 of those patients had CNS disease identified. None of the patients who received IT chemotherapy had central neurologic DLT attributable to VSLI.

Thirty-one of 36 patients (86%) received concurrent azole prophylaxis, which consisted of either fluconazole alone (n = 13) or fluconazole followed by voriconazole (n = 5) or itraconazole (n = 1), usually because of elevated hepatic transaminases. Itraconazole was initiated and later was changed to voriconazole because of gastrointestinal intolerance in 4 patients. Eight patients received voriconazole as primary antifungal prophylaxis. The type of antifungal prophylaxis did not appear to influence the incidence of peripheral neuropathy (Table 3). A higher incidence of peripheral neuropathy (76% vs 42%) was observed with a higher cumulative dose of VSLI. Of the 3 patients who experienced DLT at the 2.4 mg/m² dose level, 2 patients had received fluconazole, and 1 patient had received liposomal amphotericin for antifungal prophylaxis.

Response

In evaluating the entire cohort of 36 patients who received at least 1 dose of VSLI, the overall response rate (CR + PR) was 22% (95% CI, 10%-39%): 7 patients (19%) achieved CR, 1 patient (3%) achieved a PR, 4 patients (11%) achieved an HI, 22 patients (61%) failed to achieve an objective response (including 9 patients with progressive disease), and 2 patients (6%) were not evaluable. Responses were observed at all dose levels and in heavily pretreated patients (Table 4). CR was achieved in 2 of the 7 patients (29%) with primary refractory disease who failed to respond to induction chemotherapy regimens that included conventional VCR. Four of the 15 patients (27%) who had a first CR duration > 12 months achieved CR; 3 of 6 patients in this category achieved CR with VSLI and dexamethasone as their first salvage attempt.

Responses were categorized further (for the first and second salvage subsets; n = 28) according to expectations of CR based on relevant pretreatment characteristics that were established previously in prognostic models (Table 5).^{22,23} The largest subcategory included those with the lowest expectation of CR, as expected. Response to VSLI and dexamethasone correlated with risk group, with CR rates ranging from 13% to 50% (Table 5).

Of the 7 complete responders, 4 patients underwent allogeneic SCT after achieving remission with VSLI and dexamethasone. It is noteworthy that 1 second-salvage patient who achieved HI-PLT after 2 cycles of therapy also proceeded to allogeneic SCT with minimal bone marrow disease. The 3 patients who did not proceed to SCT in CR after VSLI and dexamethasone eventually relapsed. One patient who had precursor B-cell ALL in first relapse after receiving the hyperfractionated cyclophosphamide, VCR, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine achieved a second CR with VSLI and dexamethasone but relapsed after 2 months. One patient who had primary refractory precursor B-cell ALL (failing to respond to 2 cycles of induction chemotherapy with hyper-CVAD and rituximab) subsequently relapsed after a CR duration of 9 months. One patient who had Burkitt-type ALL in first relapse after hyper-CVAD and rituximab was unable to receive further VSLI-based therapy in CR because of grade 3 peripheral neuropathy and relapsed 2 months later with isolated CNS disease.

DISCUSSION

Outcomes with salvage chemotherapy for adults with relapsed or refractory ALL traditionally have been poor.^{22,23} Previous experience with single-agent VSLI dosed at 2 mg/m² every 2 weeks in adults with previously treated ALL was encouraging; therefore, the current phase 1 clinical trial of weekly dose-escalated VSLI and pulse dexamethasone was conducted.¹⁹ VSLI dosing was not capped, resulting in an average increase in the VCR dose of 52% (range, 31%-65%, depending on BSA and dose level) compared with conventional administration. The toxicity profile was as expected, with peripheral neuropathy (overall, 55%; grade 1/2, 47%) and medically manageable constipation (overall, 53%; grade 1/2, 47%) the most common nonhematologic toxicities attributed directly to VSLI, and the latter increased in frequency with increasing dose levels. Concurrent administration of triazole antifungal therapy may result in enhanced neurotoxicity through the inhibition of cytochrome P450-mediated metabolism of vinca alkaloids, leading to increased plasma levels of the drug.⁸ In the current study, the incidence of peripheral neuropathy appeared to be influenced by the cumulative exposure to VSLI rather than the concurrent use of itraconazole or voriconazole. The MTD was established at 2.25 mg/m² based on the DLT toxicities of grade 3 motor neuropathy, grade 4 seizure (in the setting of intracranial hemorrhage), and grade 4 hepatotoxicity observed in 1 patient each at the 2.4 mg/m² dose level.

In this study, the CR rate with VSLI and dexamethasone was 19% in the context of previous therapy with conventional VCR (all patients). It is noteworthy that 2 patients who had primary refractory disease after frontline therapy with hyper-CVAD achieved CR with VSLI-based therapy. Response was evaluated further by comparing outcomes after VSLI and dexamethasone with the expectations of CR previously established in 2 separate, large, retrospective analyses to account for the significant heterogeneity in the treatment population. In the primary refractory or first salvage setting, a previous analysis of >300 patients with previously treated ALL identified short duration of first CR (<12 months), age >40 years, and presence of circulating blasts as adverse factors.²² The rates of CR ranged from 24% to 31% after first salvage therapy with intensive regimens (eg, high-dose cytarabine combinations, hyper-CVAD). However, the CR rates varied from 9% to 47% after patients were categorized into unfavorable, intermediate, and favorable prognostic groups according to the number of adverse factors. In another recent analysis of nearly 300 patients that was confined to outcome after second salvage therapy, the overall CR rate with various treatments was 18%. However, in that analysis, the CR rate was 7% if the first CR duration was <36 months and if the pretreatment PLT count was <50 × 10⁹/L compared with a CR rate of 60% if neither feature was present.²³

In applying these prognostic models to the current study cohort, the CR rates with VSLI and dexamethasone by salvage status (29% for first salvage, 14% for second salvage) and by risk group (50% for favorable, 22% intermediate, 13% for unfavorable) were similar to those expected with intensive combination chemotherapy regimens but generally were superior to the historic experience with other investigational single agents (<10%). In this study, dexamethasone was administered concurrently with VSLI to facilitate multiple dosing because of the transient bone marrow responses observed with the previous lower intensity

single-agent VSLI salvage experience. The relative contribution of dexamethasone cannot be ascertained. It is unlikely that dexamethasone itself would induce CR in the salvage setting; however, it is possible that cyto-reduction with this agent could allow continued administration of VSLI and, thus, influence response. Regardless, the combination of VSLI plus dexamethasone appears to be an effective salvage therapy option for patients who have relapsed/refractory ALL that may permit potentially curative SCT. A phase 2 international multicenter clinical trial assessing the efficacy of weekly single-agent VSLI dosed at 2.25 mg/m² (without dexamethasone given the primary objective of response) as second salvage therapy for patients with previously treated ALL is ongoing; preliminary efficacy has been observed (S. O'Brien, unpublished results). Phase 2/3 trials that will incorporate VSLI into frontline combination chemotherapy regimens for adults with de novo ALL are under development.

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Table 1

Pretreatment Characteristics of 36 Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

Characteristic	No. of Patients (%)
Age, y	
40	25 (69)
41-59	8 (22)
60	3 (8)
Median [range], y	32 [19-62]
Women	12 (33)
ECOG performance status	
0-1	31 (86)
2-3	5 (14)
Extramedullary disease, yes	3 (8)
Leukocyte count, $\times 10^9/L$	
25	32 (89)
25-49.9	3 (8)
50	1 (3)
Circulating blasts, yes	23 (64)
Hemoglobin <10 g/dL	14 (39)
Platelet count <100 $\times 10^9/L$	24 (67)
First CR duration, mo	
0	7 (19)
1-5.9	6 (17)
6-11.9	8 (22)
12	15 (42)
Salvage attempt	
First	14 (39)
Second	14 (39)
Third or greater	8 (22)
Previous allogeneic SCT, yes	6 (17)

ECOG, Eastern Cooperative Oncology Group; CR, complete response; SCT, stem cell transplantation.

Table 2

Summary of Clinically Relevant Toxicities Attributed to Vincristine Sulfate Liposomes Injection and Dexamethasone*

Toxicity	No. of Patients (%)					All Dose Levels, n=36	
	No. With Grade 1-4 Toxicity: VSLI Dose Level, mg/m ²						
	1.5, n=5	1.825, n=3	2.0, n=3	2.25, n=18	2.4, n=7	Grade 1-2	Grade 3-4
Neurologic							
Peripheral neuropathy	1	3	2	12	2	17 (47)	3 (8)
Paresthesias	1	–	1	6	–	8 (22)	–
Altered mental status	–	–	–	1	1	–	2 (6)
Seizure	–	–	–	–	1	–	1 (3)
Gastrointestinal							
Constipation	1	2	1	10	5	17 (47)	2 (6)
Nausea	1	3	–	5	–	9 (25)	–
Abdominal pain	–	–	1	4	1	3 (8)	3 (8)
Diarrhea	1	1	–	2	–	4 (11)	–
Emesis	–	1	–	1	1	3 (8)	–
Hematologic							
Neutropenia	3	1	2	6	–	2 (6)	10 (28)
Anemia	1	–	–	4	–	2 (6)	3 (8)
Thrombocytopenia	–	–	–	4	2	1 (3)	5 (14)
Constitutional							
Fatigue	1	3	1	4	1	7 (19)	3 (8)
Pyrexia	–	1	–	3	–	4 (11)	–
Endocrine							
Hyperglycemia [†]	1	1	–	4	1	3 (8)	4 (11)
Musculoskeletal							
Myopathy [†]	–	2	2	4	2	9 (25)	1 (3)
Bone pain	–	–	–	5	–	5 (14)	–
Myalgia	–	1	–	2	–	3 (8)	–
Opthamologic							
Blurred vision [†]	1	1	–	1	–	3 (8)	–
Hepatic							
Elevations in transaminases	–	–	1	–	1	1 (3)	1 (3)
Hyperbilirubinemia	–	–	–	–	1	–	1 (3)
Cardiovascular							
Hypotension	–	–	–	2	–	1 (3)	1 (3)
Genitourinary							
Urinary retention	–	–	–	2	–	1 (3)	1 (3)

VSLI indicates vincristine sulfate liposomes injection.

* Subcategories included all grade 3-4 toxicities and grade 1-2 toxicities if ≥ 5% in frequency and excluded infections.

[†]Also attributed to dexamethasone. Peripheral neuropathy included motor and sensory, and myopathy included weakness.

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Table 3

Incidence of Peripheral Neuropathy by Azole Prophylaxis and Cumulative Dose Vincristine Sulfate Liposomes Injection

Azole	No. of Patients (%) Cumulative VSLI Dose PN Grade at 9 mg/m ² , n=19			PN Grade at >9 mg/m ² , n=17			No./Total PN
	0	1-2	3-4	0	1-2	3-4	
Fluconazole	4	3	2	–	4	–	9/13 (69)
Fluconazole-voriconazole	1	–	–	–	3	1	4/5 (80)
Voriconazole	2	–	–	2	4	–	4/8 (50)
Itraconazole-voriconazole	2	2	–	–	–	–	2/4 (50)
Fluconazole-itraconazole	–	–	–	–	1	–	1/1 (100)
None	2	1	–	1	1	–	2/5 (40)

VSLI indicates vincristine sulfate liposomes injection; PN, peripheral neuropathy.

Table 4

Complete Remission Rate by Salvage Status and Vincristine Sulfate Liposomes Injection Dose Level

Salvage Status	No. of CRs (%)					Overall, n=36
	VSLI Dose Level, mg/m ²					
	1.5, n=5	1.825, n=3	2.0, n=3	2.25, n=18	2.4, n=7	
Overall CRs	2 (40)	1 (33)	–	3 (17)	1 (14)	7 (19); 1 PR, 4 HI
Salvage attempt: No. of CRs/total						
First	1/1	0/1	–	2/8	1/4	4/14 (29)
Second	0/1	1/2	0/2; 1 HI	1/8; 1 PR, 2 HI	0/1; 1 HI	2/14 (14); 1 PR, 4 HI
Third or greater	1/3	–	0/1	0/2	0/2	1/8 (13)

VSLI indicates vincristine sulfate liposomes injection; CR, complete response; PR, partial response; HI, hematologic improvement.

Table 5

Response to Vincristine Sulfate Liposomes Injection and Dexamethasone by Prognostic Categories in First and Second Salvages Subsets

Prognostic Group *	Expected CR Rate, %	No. of Patients	No. With HI	No. of PRs	No. of CRs (%)
Favorable	45-60	4	1	–	2 (50)
Intermediate	25-30	9	1	1	2 (22)
Unfavorable	0-15	15	2	–	2 (13)

CR indicates complete response; HI, hematologic improvement; PR, partial response

* For first salvage prognostic groups, favorable characteristics included age <40 years, first CR duration >12 months, and absence of circulating blasts; intermediate characteristics included age ≥ 40 years or circulating blasts; and unfavorable characteristics included ≥ 2 unfavorable features (see Thomas 1999²²). For second salvage prognostic groups, favorable characteristics included platelet count >50×10⁹/L and first CR duration >36 months; intermediate characteristics included 1 unfavorable feature; and unfavorable characteristics included both unfavorable features (see O'Brien 2008²³).