High-dose Vincristine Sulfate Liposome Injection (Marqibo) Is Not Associated With Clinically Meaningful Hematologic Toxicity

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Abstract

Hematologic toxicity of vincristine sulfate liposome injection (VSLI) was assessed in 54 patients with metastatic cancer not known to involve bone marrow. VSLI was not associated with clinically meaningful blood count changes when dosed at 2.25 mg/m2 every 14 or 7 days. VSLI could be well suited for combination drug therapy and use in patients unable to tolerate blood cytopenias.

Background: Vincristine sulfate liposome injection (VSLI) facilitates vincristine dose intensification and densification, is active in untreated and relapsed lymphoma, and has been approved in the United States for relapsed and refractory acute lymphoblastic leukemia. Cancer- and concomitant chemotherapy-related anemia, neutropenia, and thrombocytopenia in patients with hematologic malignancy have complicated the evaluation of hematologic toxicity related to new drugs. **Patients and Methods:** We assessed the hematologic toxicity of VSLI 2.25 mg/m^2 administered every 14 (cohort 1) or 7 (cohort 2) days in 54 patients with metastatic uveal melanoma, a cancer not known to involve the bone marrow. **Results:** Cohort 2 received a greater median number of VSLI doses (6 vs. 4) within a shorter median period (5.7 vs. 8.7 weeks), resulting in a larger median cumulative exposure (22.6 vs. 17.7 mg) and near doubling of the median dose density (2.2 vs. 4.0 mg/wk) compared with cohort 1. Despite greater VSLI exposure and dose density, cohort 2 had a lower median decrease from baseline in the neutrophil count and a greater increase from baseline in the platelet count compared with cohort 1. Hematologic adverse events (AEs) were uncommon and mostly grade 1 or 2 in severity. No grade 4 hematologic AEs developed. **Conclusion:** VSLI at its approved dose resulted in a low incidence of clinically meaningful hematologic toxicity. A near doubling of the median dose density did not have an identifiable effect on the reported incidence and severity of hematologic AEs. VSLI could be well suited for use combined with myelosuppresive drugs and for patients unable to tolerate peripheral blood cytopenia.

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Introduction

The treatment of patients with heavily pretreated, advanced, relapsed, and refractory hematologic malignancies, such as Philadelphia chromosome−negative (Ph$^-$) acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL), sometimes requires the use of therapies with limited hematologic toxicity and associated peripheral blood cytopenia. The same requirement might also apply to patients with cancer and advanced age, active infection, cardiovascular disease, recent surgery, or poor performance status. Because of the near-universal, disease-related, and concomitant chemotherapy-related anemia, neutropenia, and thrombocytopenia, it has been difficult to specifically assess for, and isolate, related hematologic toxicity during the evaluation of new agents in ALL and NHL clinical trials.

Vincristine sulfate liposome injection (VSLI) is sphingomyelin- and cholesterol-based nanoparticle-encapsulated vincristine (VCR) designed to overcome the dosing and pharmacokinetic limitations of nonliposomal VCR.[1-4] In nonclinical experiments, VSLI enhanced VCR penetration and concentration in tissues and organs with fenestrated vasculature or involved in the mononuclear phagocyte system, including ALL and NHL target tissues (eg, bone marrow,

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lymph nodes, spleen) and implanted tumors.[2-6] VSLI exhibited greater milligram per milligram anticancer activity and a larger maximum tolerated dose than nonliposomal VCR.

In phase 1 dose-finding studies, VSLI was generally well tolerated and active at dose levels up to and including 2.25 mg/m^2/wk in adults and children with relapsed and refractory ALL.[7,8] All VSLI doses reflected the amount of VCR delivered and were determined by the actual patient body surface area (BSA) without dose capping at any level. Compared with the labeled dose of nonliposomal VCR of 1.4 mg/m^2, each weight-based dose of VSLI delivered $\geq$ 61% more VCR. The dose intensification facilitated by the VSLI formulation was even greater compared with the standard, fixed, "capped" 2-mg dose of nonliposomal VCR.

In phase 2 studies, VSLI dosed at 2.0 mg/m^2 every 2 weeks was effective at inducing complete and partial responses as both monotherapy and combined with rituximab in patients with advanced, relapsed, and refractory aggressive NHL.[9,10] The same dose of VSLI, combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHMP, where M = VSLI), produced remarkable response rates and long progression-free and overall survival in patients with untreated diffuse large B-cell lymphoma.[11] Weekly single-agent VSLI 2.25 mg/m^2 was approved in the United States for adults with relapsed and refractory Ph$^-$ ALL.[12]

Because previous and current VSLI development programs have focused on NHL and ALL, a different cancer patient population was required to enable assessment of the hematologic toxicity profile of the drug. Uveal melanoma almost exclusively metastasizes to the liver, lungs, and lymph nodes and is not known to directly invade the bone marrow.[13] VSLI has been reported to be active in this rare cancer.[14] In our report, we present an assessment of the hematologic toxicity profile of VSLI 2.25 mg/m^2 in patients with metastatic uveal melanoma.

Patients and Methods

Patients

Adults ($\geq$ 18 years old) with histologically or cytologically confirmed metastatic uveal melanoma were study eligible. The patients were enrolled in 2 serial cohorts. Cohort 1 patients could have received 1 previous systemic therapy. Previous treatment with immunotherapy or a cancer vaccine was allowed, provided documentation was available of disease progression. Previous treatment with hepatic arterial chemotherapy infusion or perfusion or chemoembolization of liver metastasis was allowed as long as extrahepatic disease or progression of the liver metastasis was present after regional therapy. Cohort 1 patients must not have been previously treated with a vinca alkaloid. Cohort 2 patients must not have received any previous systemic chemotherapy, immunotherapy, cancer vaccine, or hepatic arterial chemotherapy for metastatic disease.

Study eligibility required adequate liver and kidney function, as defined by a serum total bilirubin at or less than the institution's upper normal limit and a serum creatinine level of $\leq$ 2.0 mg/dL. Patients had to have adequate bone marrow function, as defined by an absolute neutrophil count (ANC) $\geq$ 1.0 $\times$ 10^9/L and platelet count $\geq$ 100 $\times$ 10^9/L. The patients had to have a Zubrod performance status of 0 to 2. Patients with known positive human immunodeficiency virus status, symptomatic central nervous system metastasis, and active serious infection not controlled by systemic antimicrobial agents were excluded.

The institutional review board at the participating centers approved the present study. This study was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice. All patients provided written informed consent.

Study Design

The data for the present analysis were collected as part of a phase 2, multicenter, single-arm, open-label study (NCT00506142). The patients in cohort 1 were treated with VSLI (Marqibo, Talon Therapeutics, Inc, South San Francisco, CA) 2.25 mg/m^2, intravenously (I.V.) by way of a peripheral or central venous catheter within 60 $\pm$ 10 minutes every 14 $\pm$ 3 days on study day 1 of each 14-day cycle. The patients in cohort 2 were treated with VSLI 2.25 mg/m^2 I.V. by way of a peripheral or central venous catheter within 60 $\pm$ 10 minutes every 7 $\pm$ 3 days on study day 1 and day 8 of each 14-day cycle. The dose calculations were determined from the BSA calculated from the actual body weight obtained at the onset of each cycle and the height obtained at study screening. No VSLI dose capping was used. The patients were treated until the appearance of unacceptable toxicity or an investigator determined that the patient was no longer benefitting from treatment. The duration of VSLI exposure was calculated from the date of the first dose plus 1 day until the date of the last dose plus 6 days to account for the extended release characteristics of the VSLI liposome.[1]

VSLI dosing modifications for hematologic toxicity were based on the ANC and platelet count assessments on the days of infusion. If the ANC was $<$ 0.5 $\times$ 10^9/L or the platelet count was $<$ 50.0 $\times$ 10^9/L, the VSLI dose was delayed for 7 days, and the counts were reassessed. If this grade 3 toxicity persisted, the VSLI was delayed for another 7 days. If the criteria for VSLI treatment were not met after 14 days of delay, the patient was removed from treatment.

Hematology Assessment

The hematologic toxicity evaluation was based on serial peripheral blood assessments and hematologic adverse event (AE) reporting using Medical Dictionary for Regulatory Activities, version 12.1 (MedDRA, McLean, VA). AE severity was graded according to the National Cancer Institute's "Common Terminology Criteria for Adverse Events, version 3.0." Bone marrow assessments were not mandated.

Statistical Analysis

Descriptive and inferential analyses were used to summarize the study data on a per cohort basis. All patients who had received $\geq$ 1 dose of VSLI (safety population) were included in this analysis. No attempt was made to combine the data from cohorts 1 and 2, because the 2 cohorts had different dosing schedules. The median, minimum, and maximum are reported for continuous variables. For qualitative outcomes, descriptive analyses were based on the distribution of these discrete outcomes and are reported as patient counts and percentages.

Results

Patient and Disease Characteristics

The baseline patient demographics and disease characteristics are listed in Table 1. A total of 54 patients, 35 in cohort 1 and 19 in