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Marqibo (Vincristine Sulfate Liposomes Injection, OPTISOME™) Concentrates Vincristine in Tumor Tissue and Lymphoid Malignancy Oriented Tissues in Tumor-Bearing Mice

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Abstract

Introduction. Vincristine sulfate (VCR) is a cell-cycle specific, lipophilic, anti-cancer drug that inhibits cell division by binding to tubulin in mitotic spindles. Marqibo is a proprietary sphingomyelin/cholesterol liposome (OPTISOME) encapsulated formulation of VCR with an extended circulating half-life and the potential for preferential malignancy targeting, exposure, and anti-cancer activity. This report evaluates the concentration and accumulation of VCR in solid tumor tissue as well as tissues frequently involved with lymphoid malignancies in tumor-bearing mice following equivalent doses of Marqibo or conventional VCR.

Methods. Mice were implanted subcutaneously with MX-1 human breast tumor tissue. When the tumor volume reached 162–485 mm^3, mice received a single intravenous dose of Marqibo, containing 1.5 mg/kg of [14C]-VCR, or 1.5 mg/kg of non-liposomal [14C]-VCR. The total radioactivity from parent compound and metabolites in tissue, VCReq, was analyzed by Quantitative Whole Body Autoradioluminography (QWBA) and tissue digestion (TD). QWBA analysis of bone marrow (BM), tumor tissue, lymph nodes, liver, and spleen required 1 flash-frozen mouse per group at various time intervals. Sagittal sections were examined histologically for radioactivity. For TD, all tissues except bone marrow were obtained from 3 mice per group prior to infusion and at selected time points. The samples were chemically digested and analyzed for radioactivity by liquid scintillation counting.

Results. QWBA analysis revealed at least two-fold higher VCReq tissue concentrations in the Marqibo-injected mice compared to the conventional VCR-injected mice.

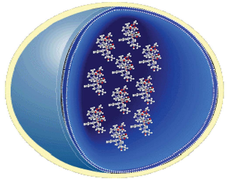
	VCReq Tissue Concentration (mcg/g) at 48 hours Post-Injection				
	BM	Tumor	Lymph	Liver	Spleen
Marqibo	0.99	1.35	1.98	0.47	6.08
VCR	0.36	0.31	--	0.13	0.76
Marqibo/VCR Ratio	2.75	4.35	--	3.61	8

The TD results are consistent with the QWBA results shown in the table. Marqibo-injected mice demonstrated a minimum 5-fold increase in VCR exposure over a 96 hour period (VCReq AUC analysis) compared to VCR-injected mice over a 48 hour period, as defined in the parameters of the study, in the implanted tumor (123 vs. 21 hr*µg/g), lymph nodes (121 vs. 16.5 hr*µg/g), liver (68.8 vs. 12 hr*µg/g), and spleen (512 vs. 68.9 hr*µg/g). Though the parameters for the AUC values may favor Marqibo, the T_{max} of all specified tissues are at least 16 times greater in Marqibo-injected mice than in VCR-injected mice (16 hrs vs. 1hr in tumor, spleen, and lymph; 4 hrs vs. 15 min. in liver; 16 hrs. vs. 15 min. in the kidney). The greatest increase in VCR exposure produced by Marqibo was observed in the spleen and lymph nodes (7.4- and 7.3-fold).

Conclusions. Marqibo resulted in targeted delivery of VCR; concentration of VCR in tumor tissue, BM, lymph nodes, liver, and spleen; and maintenance of significant tissue drug concentrations for an extended period of time compared to conventional VCR. The ability of Marqibo to target drug to these tissues and organs makes it particularly attractive as a treatment for hematologic malignancies like myeloma, lymphoma, and acute lymphoblastic leukemia (ALL). Late-stage clinical development of Marqibo in adult ALL is underway.

Background

OPTISOME, Sphingomyelin/Cholesterol Liposome Encapsulated Drug



Conventional Vincristine (VCR)

- Cell cycle-specific (M-Phase) anti-cancer drug
- Inhibits cell division by binding to tubulin in mitotic spindles
- Approved for use in the treatment of leukemias

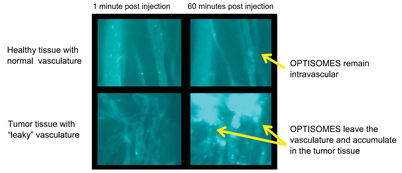
Vincristine Sulfate Liposomes Injection (Marqibo, VSLI)

- A sphingomyelin and cholesterol liposome (Optisome) encapsulated formulation of VCR
- The encapsulation results in a nanoparticle delivery system with an extended circulating half-life

Optisomes have the potential to deliver chemotherapy safely and effectively

- Sphingomyelin/cholesterol interaction results in a tightly packed lipid bilayer
- 100 nm mean diameter
- ≈ 10,000 drug molecules per liposome
- Aqueous core at pH = 4.0 enables high concentration loading and prevents payload hydrolysis
- Retain drug long enough to reach areas of tumor involvement
- Predictable first-order drug release rate (T½ ≈ 24 hours)

OPTISOMES Accumulate in Tumors



Intravital microscopy following administration of fluorescein-labeled vincristine OPTISOMES

Methods & Materials

- MX-1 tumors from four in vivo passages in mice were harvested when tumor diameter reached 10-15 mm or tumor volume reached 300-600mm^3
- Total pool of 156 female Crl:nu/nu (CD-1®)BR nude mice
  - 130 mice were implanted subcutaneously with MX-1 human breast tumor tissue
  - 26 mice were not implanted with tumor (tumor-free)
- On the day of treatment, tumors were measured and mice with tumor volumes ranging from 165–466 mm^3 were selected for inclusion into the study
- Treatments were administered as a single bolus injection of 1.5 mg/kg of [14C]-VCR or Marqibo dose on Days 18, 19 or 20 (when tumor volumes reached 160 – 470 mm^3)
- Following randomization, mean tumor volumes for all treatment groups ranged from 223-350 mm^3
- VCReq was analyzed using TD and QWBA
  - TD: tumor tissue was obtained from 3 mice/group prior to infusion, 4, 16 and 48 hours post-infusion. Samples were analyzed by liquid scintillation counting.
  - QWBA: 1 flash-frozen mouse/group prior to infusion, 4, 16 and 48 hours post-infusion. Samples were analyzed histologically for radioactivity.

Results

Comparison of AUC_{last} Following Administration of Marqibo and VCR (TD Analysis)

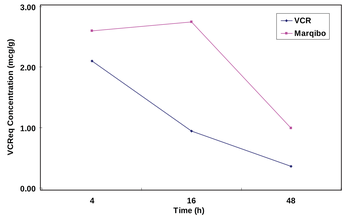
Tissue	AUC_{last} Marqibo (h*mcg/g)	AUC_{last} VCR (h*mcg/g)	Ratio of Marqibo to VCR
Skin	42.5	2.13	**20.0**
Spleen	512	68.9	**7.4**
Lymph Nodes	121	16.5	**7.3**
Tumor	123	21.0	**5.9**
Liver	68.8	12.0	**5.7**
Kidney	66.2	12.2	**5.4**
Heart	19.4	8.82	**2.2**
Lung	33.1	21.9	**1.5**
Muscle	6.11	5.28	**1.2**
Gall Bladder	228	220	**1.0**

Summary of QWBA VCReq Distribution in Tumor-Bearing Mice Following Administration of Either 1.5 mg/kg Marqibo or VCR

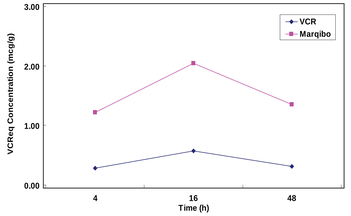
Tissue	VCReq Concentration (mcg/g)					
	VCR			Marqibo		
	4 h	16 h	48 h	4 h	16 h	48 h
Bone Marrow	2.10	0.94	0.36	2.60	2.75	0.99
Liver	0.53	0.16	0.13	3.67	1.05	0.47
Lymph Nodes	-	-	-	-	-	1.98
Spleen	2.22	1.21	0.76	8.56	6.45	6.08
Tumor	0.28	0.57	0.31	1.22	2.04	1.35

Summary of TD VCReq Distribution in Tumor-Bearing Mice Following Administration of Either 1.5 mg/kg Marqibo or VCR

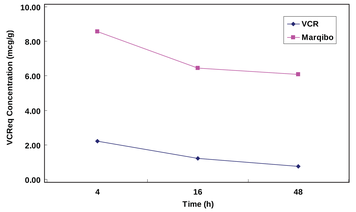
Tissue	VCReq Concentration (mcg/g)					
	VCR			Marqibo		
	4 h	16 h	48 h	4 h	16 h	48 h
Liver	0.70	0.10	0.08	2.49	0.95	0.66
Lymph Nodes	0.80	0.28	0.11	1.66	2.77	1.23
Spleen	2.43	1.33	0.53	5.26	10.78	7.83
Tumor	0.46	0.36	0.34	1.12	2.09	1.39



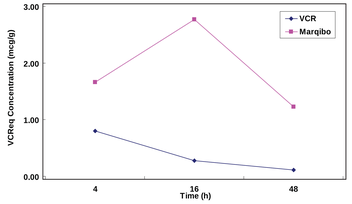
VCReq Concentration in Bone Marrow (QWBA Analysis)



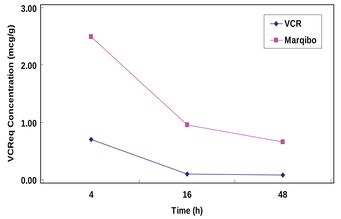
VCReq Concentration in Tumor Tissue (QWBA Analysis)



VCReq Concentration in the Spleen (QWBA Analysis)



VCReq Concentration in the Lymph Nodes (TD Analysis)



VCReq Concentration in the Liver (TD Analysis)

Conclusions

- Lymphoid malignancy oriented tissue VCReq concentrations and overall exposures were greater in Marqibo-treated than conventional vincristine-treated mice
- Intra-tumor vincristine concentrations were greater in Marqibo-treated mice compared to conventional vincristine-treated mice at all comparable time points (4, 16, and 48 h) resulting in greater vincristine exposure
- Marqibo adminstration resulted in a 3-fold increased concentration of vincristine in bone marrow at 48 hours and maintained significant tissue concentrations for several days compared to conventional vincristine
- Though the parameters for the AUC values may favor Marqibo, the T_{max} of all specified tissues are at least 16 times greater in Marqibo-injected mice than in VCR-injected mice (16 hrs vs. 1hr in tumor, spleen, and lymph; 4 hrs vs. 15 min. in liver; 16 hrs. vs. 15 min. in the kidney)
- This unique characteristic of Marqibo (optisome-encapsulated vincristine) resulted in greater targeted drug exposure and the potential for enhanced anti-tumor activity without increased toxicity
- Late stage clincial development of Marqibo in adult ALL is underway

Disclosure

- There are no relevant conflicts of interest to disclose

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