

Vinorelbine Liposomes Injection Results in Greater Tumor Drug Exposure Compared to Conventional Vinorelbine in Tumor-Bearing Nude Mice

Steven R. Deitcher¹, Pieter Cullis², May Wong¹, Gavin S. Choy¹

¹Hana Biosciences, Inc., South San Francisco, CA, USA; ²University of British Columbia, Vancouver, Canada

Abstract

Introduction. Conventional vinorelbine tartrate (VRL) is a lipophilic, cell-cycle-specific anticancer agent that inhibits tumor cell growth by disrupting microtubule assembly during metaphase. Alcrest™ (Vinorelbine Liposomes Injection, VLI) is a proprietary sphingomyelin/cholesterol liposome (OPTISOME™) encapsulated formulation of VRL with an extended circulating half-life and the potential for enhanced tumor tissue targeting, exposure, and antitumor activity. This study evaluated and compared the pharmacokinetic (PK) profiles and tissue distributions (TD) of Alcrest and VRL in tumor-bearing CD-1 female nude mice.

Methods. Mice were subcutaneously implanted with MX-1 human breast tumors. When tumor volumes reached 150 mm³, twenty-four mice per group received a single intravenous (IV) bolus dose of 20 mg/kg (60 mg/m²) of either VRL (H-VRL) or Alcrest (H-Alcrest) via the tail vein in a vehicle volume of 10 µL/g body weight. Blood/plasma and tissue samples (gall bladder/bile, heart, kidneys, liver, lungs, muscle, ovaries, small intestine, spleen, and tumor) were collected at 5 minutes, 1 hour, 4 hours, 8 hours, 24 hours, and 96 hours post dosing. The total radioactivity from parent compound and metabolites in tissue, vinorelbine equivalents (VRL_{eq}), was analyzed by liquid scintillation counting.

Results. The concentrations of VRL_{eq} in blood/plasma were higher after administration of Alcrest resulting in higher AUC₀₋₉₆ in Alcrest-treated mice compared to VRL-treated mice. The steady state volume of distribution (V_{ss}) and clearance (CL) were lower for Alcrest compared to VRL, supporting slower distribution and removal of Alcrest from the plasma compartment. The TD profile of Alcrest showed that, depending on the tissue, VRL_{eq} concentrations peaked at 4 or 8 hours compared to VRL T_{max} at 5 minutes or 1 hour. Tumor AUC₀₋₉₆ values (h*mcg/g) for VRL_{eq} were 1166 in the Alcrest group and 123 in the VRL group. The AUC₀₋₉₆ for Alcrest was 9.5-fold greater in the tumor, 7.0-fold higher in spleen, 2.4-fold higher in ovaries and 1.0–1.6-fold higher in most other tissues (lower in lung) compared to the AUC₀₋₉₆ for conventional VRL. The greatest amount of radioactivity as a percent of injected dose (%ID) following Alcrest was found in liver > spleen > tumor while following VRL the greatest %ID was in liver > kidneys > lungs > small intestine. The %ID following Alcrest peaked at 4 to 8 hours before declining except in tumor where %ID peaked at 24 hours and remained constant for up to 96 hours.

Conclusions. Optosomal encapsulation of VRL, Alcrest, protects the drug from initial rapid distribution observed with conventional VRL and provides longer drug retention in the circulation. Alcrest results in targeted delivery of drug, accumulation of drug in tumor tissue, and gradual drug release over several days. These unique characteristics result in greater tumor drug exposure and the potential for enhanced anti-tumor activity without increased toxicity. Human clinical trials are ongoing at this time.

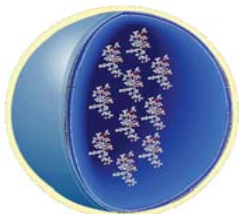
Introduction

Conventional Vinorelbine Tartrate (VRL)

- Cell-cycle-specific (M-phase) anti-cancer drug
- Inhibits tumor cell growth by disrupting microtubule assembly
- Approved for usage in ambulatory patients with unresectable, advanced non-small cell lung cancer

Optosomal Vinorelbine (Alcrest)

- A sphingomyelin and cholesterol liposome (OPTISOME) encapsulated formulation of VRL
- Encapsulation results in a nanoparticle delivery system with an extended circulating half-life and anticipated preferential delivery to sites with "leaky vessels" or many macrophages



OPTISOME, Sphingomyelin/Cholesterol Liposome Encapsulated Drug

Study Objectives

- To evaluate and compare the pharmacokinetic (PK) profiles of Alcrest and VRL in tumor-bearing CD-1 female nude mice
- To evaluate and compare the tissue distributions (TD) of Alcrest and VRL in tumor-bearing CD-1 female nude mice

Methods & Materials

- Tumor bearing CD-1 female nude mice were supplied by Charles River Laboratories
- MX-1 tumor cells were purchased from the National Cancer Institute Tumor Repository
- Tumor fragments were passaged *in vivo* for three (3) cycles and harvested when tumor diameter reached 10-15 mm (300-600 mm³)
- Tumor fragments were subcutaneously implanted into eight (8) week old mice
- On Day 19, 20 or 22 post-implantation, mice with a tumor volume of at least 150 mm³ (24 mice per group), received a single bolus dose of 20 mg/kg (60 mg/m²) of either VRL (H-VRL) or Alcrest (H-Alcrest) via tail vein injection
- Blood/plasma (0.5 mL) and tissue samples (gall bladder/bile, heart, kidneys, liver, lungs, muscle, ovaries, small intestine, spleen, and tumor) were collected at 5 minutes, 1 hour, 4 hours, 8 hours, 24 hours, and 96 hours post-dose (4 mice per group per timepoint)
- Total radioactivity from parent compound and metabolites in tissue, VRL_{eq}, was analyzed by liquid scintillation counting
- Noncompartmental PK and TD analyses were performed using WinNonlin Version 4.0.1

Results

- V_{ss} and CL were smaller for Alcrest compared to VRL, supporting slower distribution and removal of Alcrest from the plasma compartment
- Depending on the tissue, VRL_{eq} concentrations peaked at 4 or 8 hours following Alcrest compared to VRL T_{max} at 5 minutes or 1 hour
- AUC₀₋₉₆ for Alcrest was 9.5-fold greater in the tumor, 7.0-fold higher in spleen, 2.4-fold higher in ovaries and 1.0–1.6-fold higher in most other tissues compared to the AUC₀₋₉₆ for conventional VRL
- The greatest amount of radioactivity as a percent of injected dose (%ID) following Alcrest was found in liver > spleen > tumor while following VRL the greatest %ID was in liver > kidneys > lungs > small intestine
- The %ID following Alcrest peaked at 4 to 8 hours before declining except in tumor where %ID peaked at 24 hours and remained constant for up to 96 hours

Blood and Plasma Pharmacokinetic Parameters Based on Noncompartmental Analysis

Parameter	Alcrest (Blood)	VRL (Blood)	Alcrest (Plasma)	VRL (Plasma)
Average Dose (mcg)	525	524	525	524
C _{max} (mcg/mL)	194	3.78	293	3.21
t _{1/2α} (h)	3.69	1.79	3.88	1.67
AUC ₀₋₉₆ (h*mcg/mL)	1315	20.1	2521	20.8
V _{ss} (mL)	2.49	839	1.36	1373
CL (mL/h)	0.4	26.1	0.208	25.2
MRT _{last} (h)	6.13	16.1	6.48	20

Disposition Kinetics of VRL_{eq} in the Tissues of MX-1 Tumor-Bearing Mice Following Administration of 20 mg/kg of Alcrest

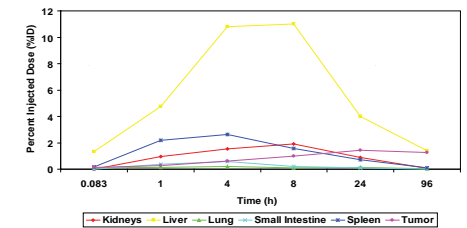
Tissue	T _{max} (h)	C _{max} (mcg/g)	AUC ₀₋₉₆ (h*mcg/g)	T _{1/2} (h)	MRT _{last} (h)
Spleen	4	151.2	5303	23.6	21.8
Gall Bladder	8	151.3	2735	19	12.6
Liver	8	53.7	1668	47.5	25.3
Kidneys	8	38.5	1296	18.6	19.7
Tumor	8	15.2	1166	106.5	40.7
Ovaries	4	10.6	435	30	25.6
Lungs	4	7.1	351	37	27.9
Small Intestine	4	15.6	335	17.9	16.7
Heart	4	5.6	198	23.1	21.7
Muscle	4	1.6	71	27.5	24.6

Disposition Kinetics of VRL_{eq} in the Tissues of MX-1 Tumor-Bearing Mice Following Administration of 20 mg/kg of VRL

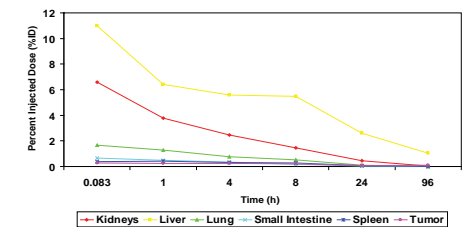
Tissue	T _{max} (h)	C _{max} (mcg/g)	AUC ₀₋₉₆ (h*mcg/g)	T _{1/2} (h)	MRT _{last} (h)
Spleen	1	30.4	757	21.1	18.9
Gall Bladder	1	356.6	1988	23.5	8.7
Liver	0.083	48.9	1016	55.4	26.7
Kidneys	0.083	132.1	1106	18.3	14.3
Tumor	1	2.9	123	80.4	37.3
Ovaries	1	11.7	184	30.8	21.9
Lungs	0.083	59	577	26.1	12.2
Small Intestine	0.083	24.5	227	23.4	11.8
Heart	0.083	40.8	148	29.1	11.1
Muscle	0.083	9	70	25.9	12.1

Comparison of AUC₀₋₉₆ Following Administration of Alcrest and VRL

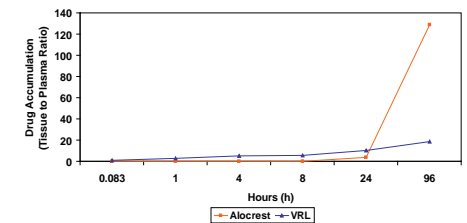
Tissue	AUC ₀₋₉₆ Alcrest (h*mcg/g)	AUC ₀₋₉₆ VRL (h*mcg/g)	Ratio of Alcrest to VRL
Tumor	1166	123	9.5
Spleen	5303	757	7
Ovaries	435	184	2.4
Liver	1668	1016	1.6
Small Intestine	335	227	1.5
Gall Bladder	2735	1988	1.4
Heart	198	148	1.3
Kidneys	1296	1106	1.2
Muscle	70.9	69.6	1
Lung	351	577	0.6



Percent Injected Dose Following Administration of Alcrest



Percent Injected Dose Following Administration of VRL



Relative Accumulation of Drug in Tumor Following Administration of Alcrest and VRL

Conclusions

- Optosomal encapsulation of vinorelbine (Alcrest) protects the drug from the initial rapid distribution observed with conventional vinorelbine and provides longer drug retention in the circulation and tumors
- Alcrest results in targeted delivery of drug, accumulation of drug in tumor tissue, and gradual drug release over several days. These unique characteristics result in greater tumor drug exposure and the potential for enhanced anti-tumor activity without increased toxicity
- Human clinical trials are ongoing at this time