A prospective multi-center phase II trial of systemic ADH-1 in combination with melphalan via isolated limb infusion in patients with advanced extremity melanoma

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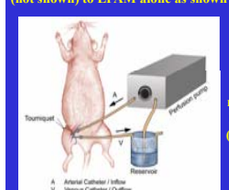
Abstract

Isolated limb infusion with melphalan (ILI-M) dosing corrected for ideal body weight (IBW) is a well tolerated treatment for patients with in-transit extremity melanoma with an approximate 30% CR and 44% overall response rate. ADH-1 is a cyclic pentapeptide that disrupts N-cadherin adhesion complexes. ADH-1 when given systemically in a preclinical model with regional melphalan demonstrated synergistic antitumor activity and had minimal toxicity in a Phase I trial with M-ILI. AJCC stage IIIB or IIIC extremity melanoma patients were treated with 4000mg of ADH-1 administered systemically on Day 1 and 8 in addition to standard dose M-ILI corrected for IBW on Day 1. 45 patients were enrolled over 18 months at 4 institutions. Treatment was well tolerated and there were no limb losses or compartment syndromes.

Introduction

In up to 10% of extremity melanoma cases, lesions recur locally, confined to the extremity in a pattern called in-transit disease. The delivery of regional chemotherapy namely L-Phenylalanine Mustard (LPAM or melphalan) to an isolated extremity has been a treatment option since the 1950's with response occurring in 40-80% of patients. Isolated limb infusion (ILI) has recently been developed by the Sydney Melanoma Unit as a simple, less invasive technique for delivering chemotherapy to an isolated extremity. A schematic of ILI is shown in Figure 3.

Malignant transformation in melanoma is characterized by a phenotype "switch" from E-cadherin to N-cadherin which is associated with increased motility and invasiveness of the tumor and altered signaling leading to decreased apoptosis. We hypothesized that disruption of N-cadherin binding using a novel pentapeptide (ADH-1) could sensitize melanoma tumors to the cytotoxic effects of LPAM. In a pre-clinical model, N-cadherin expressing human melanoma-derived cell lines were used to generate xenografts in animal models to study isolated limb infusion with melphalan. Previous work in our lab demonstrated the combination of systemic ADH-1 with LPAM via ILI was dramatically and significantly ($p<0.005$) more effective than LPAM alone in xenografts that were sensitive to LPAM and in xenografts that were resistant (not shown) to LPAM alone as shown in Figure 1.



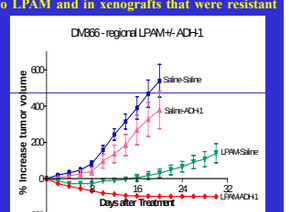


Figure 1: ILI model in rats (left). Tumor response post ADH-1 and LPAM via ILI in DM366 (right), a high N-cadherin expressing xenograft).

We hypothesize that the mechanism of ADH-1 chemosensitization may be related to the effects of ADH-1 on endothelial cell permeability. In Figure 2 below, marked extravasation of Evans Blue Dye was seen in rat limbs bearing DM448 tumor treated with ADH-1.

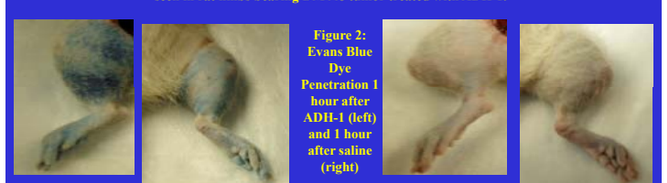


Figure 2: Evans Blue Dye Penetration 1 hour after ADH-1 (left) and 1 hour after saline (right)

Methods

Patients

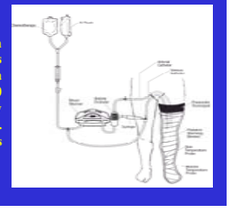
Major Inclusion Criteria: 1) ≥18 yrs age 2) histologic AJCC Stage IIIB or IIIC extremity melanoma 3)measurable cutaneous disease distal to tourniquet placement 4) palpable femoral/axillary pulse 5) ECOG status 0 or 1

Major Exclusion Criteria: 1) received ADH-1 previously, previous ILI-M allowed 2)received other therapies within 4 wks of 1st ADH-1 administration 3)Stage IV disease 4) history of tumors that had shown evidence of active bleeding within 12 weeks prior to first ADH-1 administration

Intervention

ADH-1 4000mg IV Within 8 Hours of ILI → ILI with LPAM → ADH-1 4000mg IV 8 Days Post ILI

Figure 3: Schematic of Isolated Limb Infusion: Percutaneous catheters are placed into the vein and artery of the affected limb. A tourniquet is then inflated for isolation. LPAM is infused via the arterial catheter and circulated for 30 minutes. Venous outflow is accomplished by manual extraction. The blood is not oxygenated. A wash-out using isotonic crystalloid solution is performed at the conclusion.



Results-1

Duke → 24
MD Anderson Cancer Center → 14
Moffitt Cancer Center → 6
University of Florida → 1

TOTAL = 45 procedures

Table 1: Patient Characteristics

	Number	%
Age Range/ Median	29-89/61	
Male	19	42
Female	26	58
AJCC Stage		
IIIB	17	38
IIIC	28	62
Disease Burden		
High	12	27
Low	33	73
Previous ILI/HILP	11	25
N-cadherin positive	19	42

Results-2

Figure 5: Response was determined at 3 months according to RECIST modified for cutaneous lesions.

45 total treatments

CR=Complete Response
PR=Partial Response
SD=Stable Disease
PD=Progressive Disease

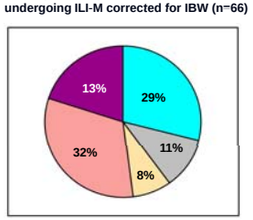
CR in 16 patients	PR in 10 patients	SD in 6 patients	PD in 9 patients	4 patients N/A
36%	22%	13%	20%	9%

Patterns of Complete Response

A: Complete Disappearance

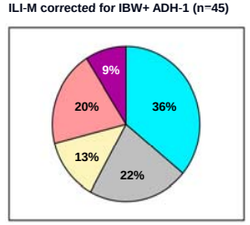
B: Persistent Pigment

Response in patients from 8 centers undergoing ILI-M corrected for IBW (n=66)



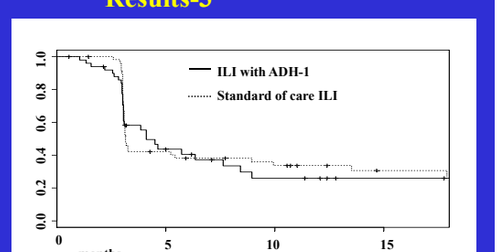
=CR
=PR
=SD
=PD
=NA

Response in study patients undergoing ILI-M corrected for IBW+ ADH-1 (n=45)



Results-3

Figure 6: Time to progression (TTP) curves. The median TTP for patients in this study is 4.1 months with 95% CI of (3.1 – 7.6); the median TTP for the Duke ILI-M alone is 3.2 months with 95% CI of (3.1 – 9.9) . P=0.82



Results-5

Most commonly reported, per patient (n=45), toxicity assessed by NCI's CTCAEv3. There was only 1 clinical grade IV toxicity.

AE Term	Grade I	II	III	IV
Serologic Toxicities				
CPK elevation	4	4	4	4
anemia	5	4	4	
elevated LFTs	7		1	
thrombocytopenia	4			
hypoalbuminemia	2	5		
hypocalcemia	5	1		

AE Term	Grade I	II	III	IV
Clinical Toxicities				
rash/derm	15	4		
pain	12	9	1	
edema	13	3		
nausea	5	1		
fatigue	11			
pruritus	4			
vomiting	4	1		
neuropathy	6	1		
erythema	4			
blistering		3		
constipation	5			
petechiae	1	1		
hypotension		2		
arrhythmia			2	
cellulitis			2	
arterial injury				1

Conclusions

- This is the first prospective multi-center study of ILI and the first to use a combination therapy with a systemic targeted agent.
- Systemic ADH-1 administered pre and post ILI with melphalan is well tolerated in patients with regionally advanced melanoma.
- Although overall response rates at 3 months were better in patients receiving ADH-1 than our historical group using ILI with melphalan alone, there was no significant difference between time to progression curves.
- The 36% complete response rate exceeded our expectations in this group of heavily pre-treated patients which warrants further investigation of this therapy.

Future Directions

- Complete correlative analysis of drug PK and N-cadherin expression to better understand clinical response data
- Understand more clearly the mechanism of action of ADH-1 seen in pre-clinical models
- Determine more optimal drug dosing of ADH-1 in both ILI and hyperthermic isolated limb perfusion (HILP) to parallel pre-clinical studies
- Explore applications of targeting N-cadherin in the systemic treatment of melanoma