Treatment of HIV-Associated Kaposi's Sarcoma with Aldoxorubicin

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Abstract

***Background*:** In the past Kaposi's sarcoma (KS) was a major cause of morbidity and mortality in HIV-infected individuals. Risk factors are defined by the TIS scoring system (tumor extent, immune status, symptom score, 0 or 1 each) with scores > / = 1 = increased risk. Current treatments for KS involve either liposomal doxorubicin(LD) or paclitaxel (P), each with up to 50% grade 3/4 AEs. Aldoxorubicin (A) is doxorubicin attached to a pH sensitive linker that binds covalently and specifically to albumin. We have treated 15 patients with KS with low dose A and monitored tumor response, adverse events and accumulation of A in the tumor and peritumor tissue. ***Methods*:** Of the 15 patients entered in the study 4 had received prior D, 1 prior LD and 1 prior P. Patients were administered either 50 mg/m^2 A (1), 100 mg/m^2 A (7) or 150 mg/m^2 A (7) every 3 weeks by IV infusion. Tumor response and adverse events were recorded. Presence of KS human herpes virus (KS HHV-8; LANA+ cells) in biopsies was detected by immunofluorescence. Uptake of A in into biopsies of tumor and peritumoral tissue was assessed via a validated HPLC method. ***Results*:** 7 patients had a maximum TIS score of 3, 4 had a TIS score of 2, and 4 had a TIS score of 1. All were males. Average age was 35 years (23-57); 8 black and 7 white. Median number of cycles administered was 6 (1-9). Median exposure for the 100 mg/m^2 dose was 614 mg/m^2 Dequivalents (Deq), (range 130-1261 mg/m^2 Deq); for 150 mg/m^2 dose it was 1094 mg/m^2 Deq (range 234-1787 mg/m^{2}Deq). 4 subjects experienced grade 3/4 neutropenia; other grade 3/4 AEs were rare. 2 SAEs were treatment related (neutropenia, paresthesia). Best responses included 10 PRs, 1 SD and 1 PD of 12 evaluable patients. Average concentration of A in tumors was 31.4 +/- 4.6 ng/mg tissue and in the peritumoral tissue 23.5 +/- 7.2 ng/mg tissue. 5 patients were evaluated for LANA+ cells had either complete or partial disappearance of infected cells. All patients with extensive pulmonary lesions had either a CR or PR. ***Conclusions*:** A is an active drug for the treatment of HIV-associated KS even in patients with extensive disease and who had received prior doxorubicin therapy. It is detected in tumor tissue and is associated with marked improvement in pulmonary symptoms and decreases in HHV-8 infected KS cells.

Background

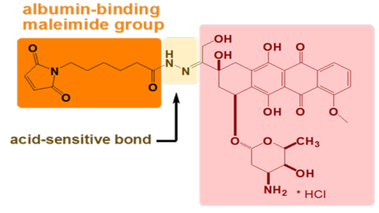
***KS trials involving urban, minority-predominant cohorts with moderate to severe disease (low CD4# T-cell counts and visceral KS) demonstrate toxicity and lack of efficacy with standard therapies*:**

- In a trial comparing paclitaxel (PTX) to pegylated liposomal doxorubicin (PLD; Doxil®) was conducted in patients with advanced KS who had not received prior systemic cytotoxic chemotherapy[1]:
  - CR +PR response rates: 57% (PTX), 47% (PLD)
  - Median PFS: 17.5 months (PTX), 12.2 months (PLD)
  - Grade 3+ adverse events:
    - CD4: 50% (PTX), 29% (PLD)
    - Neutropenia: 58% (PTX), 37% (PLD)
    - Overall: 84% (PTX), 66% (PLD)
- CR + PR response rate of 56% was observed in patients receiving PTX for advanced KS following lack of response to initial chemotherapy[2]

Aldoxorubicin

- Aldoxorubicin is a prodrug of the anticancer agent doxorubicin which is derivatized at its C-13 keto-position with a thiol-binding spacer molecule (6-maleimidocaproic acid hydrazide).
- Aldoxorubicin is quantitatively and selectively bound to the cysteine-34 position of endogenous albumin within a few minutes. The reaction follows second-order kinetics.[3]
- Aldoxorubicin is significantly less cardiotoxic in a chronic rat model when compared to doxorubicin at an equitoxic dose.[4] Aldoxorubicin has not been associated with any clinically significant cardiotoxicity in over 200 patients treated with up to 4 g/m2 of doxorubicin equivalents.
- In humans, aldoxorubicin has a mean circulating $t_{1/2}$ of 20.1-21.1 h, a narrow mean volume of distribution of 3.96-4.08 L/m^2, and a slow mean clearance rate of 0.136-0.152 L/h/m^2.[5]
- In a first-line soft tissue sarcoma study, aldoxorubicin significantly increased PFS, PFS at 6 months and ORR compared to doxorubicin, as well as improved OS.[6]

Structure of Aldoxorubicin



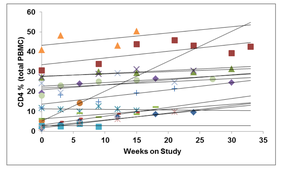
Study Design

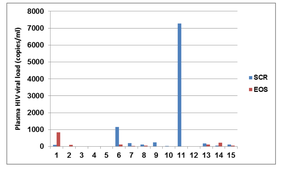
- Open-label phase 2 pilot study evaluating the preliminary efficacy and safety of aldoxorubicin administered at 50, 100, or 150 mg/m^2 (36.5, 75 and 110 mg/m^2 doxorubicin equivalents) by IVI every 21 days until evidence of tumor progression, unacceptable toxicity, withdrawal of consent, or at the discretion of medical oncologists
- Staging assessed using the AIDS Clinical Trials Group (ACTG) tumor, immune system, systemic illness (TIS) criteria.
- Response to therapy, skin and visceral lesions evaluation at (baseline, prior to Cycle 4, and end of study to evaluate visceral lesions):
  - skin lesions (number, size, and nodularity)
  - chest computed tomography (CT)
  - abdominal magnetic resonance imaging (MRI)
- Safety monitoring:
  - physical examination, KPS, ECOG performance
  - laboratory evaluation (serum chemistries, complete blood count)
  - cardiac ECHO and ECG
- Laboratory monitoring:
  - intratumoral LANA expression (dots/cell)
  - tumor vs non-tumor skin Aldoxorubicin concentrations

Patient Profile

Patient	Initial CD4 cells/mm^3 (%)	TIS	Prior Doxil (mg/m^2)
001	18 (1.5)	T1,I1,S1	120
002	362 (31)	T1,I0,S0	180
003	400 (27)	T1,I0,S1	None
004	444 (27)	T0,I0,S1	None
005	98 (11.7)	T1,I1,S1	160
006	40 (5.3)	T1,I1,S1	None
007	160 (11.8)	T1,I1,S1	None
008	49 (2.8)	T1,I1,S1	None
009	27 (6.4)	T1,I1,S1	20
010	276 (19.4)	T1,I0,S0	170
011	36 (2.8)	T1,I1,S1	None
012	860 (24.2)	T0,I0,S1	None
013	252 (24.2)	T1,I0,S1	None
014	48 (1.9)	T1,I1,S1	None
015	630 (18.1)	T1,I0,S1	None

HIV Parameters on Study



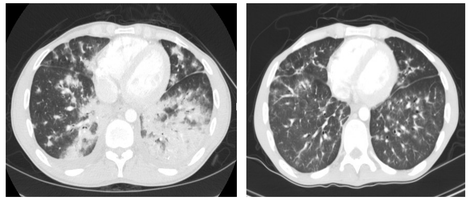


Results – Overall Assessment

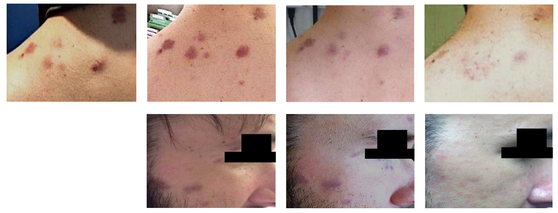
	Overall Assessment*	
Patient	Cycle 4	EOS
001	PR	SD
002	PR	PR
003	SD	SD
004	SD	PR
005	PR	ND
006	ND	PD
007	PR	PR
008	PR	PR
009	PR	SD
010	PR	PR
011	ND	PR
012	PR	PR
013	PR	PR
014	PR	**
015	PR	**

*Assessments based on skin lesions, target lesions, quality of life
**Still on study

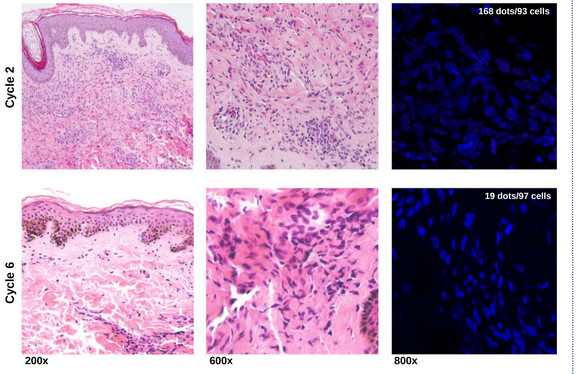
Patient 006



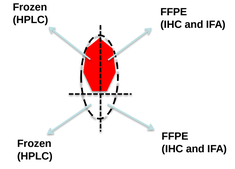
Patient 009



Patient 009



Skin Biopsy Schematic



Intratumoral Drug Concentrations (ng/mg tissue)

Patient	Cycle	KS Tissue	Peritumoral skin
001	2	32.3	*
	4	16.4	*
002	2	0	*
	4	31.4	21.0
	6	24.6	15.3
003	2	11.2	0
	6	13.6	16.6
004	2	30.7	*
	6	18.9	*
005	2	35.0	*
	4	25.4	30.1
007	2	20.1	*
008	2	87.1	61.5
009	2	48.4	20.0
	6	27.8	18.1
010	2	56.1	39.1
	6	49.4	44.1
011	2	63.7	25.5
013	2	50.5	46.5
015	2	37.8	36.9
	6	44.2	42.8

* Tumor-free skin was not confirmed on histopathologic assessment

Grade 3+ Adverse Events Related to Aldoxorubicin

AEs: left leg abscess, leukopenia, WBC decreased, hypoalbuminemia, hyperbilirubinemia, anemia, decreased neutrophil count
SAEs: paresthesias, neutropenia, death (#006, visceral KS progression)

Conclusions

- Aldoxorubicin is thus far very well-tolerated, with grade 3+ AE rates for CD4 T-cells (0%), neutropenia (22%), and overall AEs (44%) comparing favorably with AE rates from other trials enrolling KS patients representing urban, minority-predominant populations.
- 11/13 (85%) at cycle 4 demonstrated PR to aldoxorubicin, and 8/12 (67%) demonstrated PR to aldoxorubicin at EOS.
- 5/6 (83%) patients receiving aldoxorubicin and for whom data are available exhibited reduced intratumoral viral loads during therapy.
- Higher doxorubicin concentrations were demonstrated within KS lesions relative to non-tumor skin for 12/14 (86%) patients for whom adequate non-tumor tissue was available for analysis.

References

1. Cianfrocca M, Lee S, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kapsoi's sarcoma: Evidence for symptom palliation from chemotherapy. *Cancer*. 2010, 116(16): 3969-3977.
2. Tulpule A, Groopman J, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. *Cancer*. 2002, 95(1):147-154.
3. Kratz F, Beyer U. Serum proteins as drug carriers of anticancer agents: a review. *Drug Delivery*. 1998, 5:281-299.
4. Lebrecht D, Geist A, Ketelsen U, et al. The 6-maleimidocaproyl hydrazone derivative of doxorubicin (DOXO-EMCH) is superior to free doxorubicin with respect to cardiotoxicity and mitochondrial damage. *Int J Cancer*. 2007, 120:927-934.
5. Mita M, Natale R, et al. Pharmacokinetic study of aldoxorubicin in patients with solid tumors. *Invest New Drugs*. On-Line 12Nov2014.
6. Chawla S, Chua V, et al. A phase 1b/2 study of aldoxorubicin inpatients with soft tissue sarcoma. *Cancer*. 2015, 121(4):570-579.

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Disclosures
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