Longer Term Cardiac Safety of Aldoxorubicin

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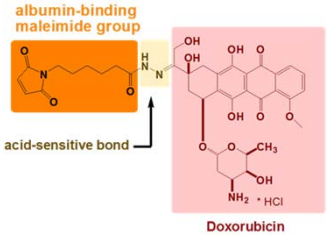
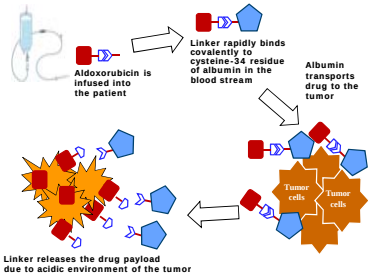
Abstract

BACKGROUND: Aldoxorubicin (6-maleimidocaproic acid hydrazide) is a novel prodrug of doxorubicin that binds to the thiol group of cysteine-34 amino acid in circulating albumin. The circulating albumin-drug conjugate preferentially accumulates within tumors, bypassing uptake by most normal tissues, including the heart, liver, kidneys and GI tract. Doxorubicin is released in the acidic tumor environment, either intra-or extra-cellularly, thus avoiding the cumulative toxicity that can occur with doxorubicin treatment. ***METHODS:*** Aldoxorubicin has been investigated in clinical trials since 2011. We reviewed data on the cardiotoxicity of aldoxorubicin from 3 phase 1 studies and 1 phase 2b study (142 patients). Either MUGA and echocardiograms were administered at baseline then periodically thereafter (usually every 2 months) until either study withdrawal or death. All patients had normal cardiac function at baseline with LVEF > 45% in some studies and 50% in others. Prior exposure up to 225 mg/m^2 of doxorubicin was permitted. ***RESULTS:*** The dose range of aldoxorubicin was 175-350 mg/m^2 administered i.v. every 3 weeks (equivalent to 130-260 mg/m^2 doxorubicin per cycle). There were 126 evaluable patients who received 1-21 cycles of treatment. While 14% of patients demonstrated a ≥ 10% drop in LVEF, 21% had a ≥ 10% increase in LVEF. No patient exhibited a decrease in LVEF that was below 50% of their institution's normal value. Patients have received up to 5,439 mg/m^2 of doxorubicin equivalents, or 12 times the peak cumulative dose of standard doxorubicin, without any evidence of cardiotoxicity. ***CONCLUSION:*** Despite administering cumulative doses of over 1500 mg/m^2 to the majority of the 126 evaluable patients in these clinical studies, aldoxorubicin has shown no evidence of cardiotoxicity, distinguishing it from doxorubicin itself.

Structure of Aldoxorubicin



Proposed Mechanism of Action



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.
- Aldoxorubicin was superior to free doxorubicin in several human tumor xenograft models.[1]
- Aldoxorubicin is significantly less cardiotoxic in a chronic rat model when compared to doxorubicin at an equitoxic dose.[2]
- 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.
- Plasma concentrations of free doxorubicin and doxorubicinol were only small fractions of the plasma concentration of albumin-bound doxorubicin. Therefore, almost all doxorubicin in the circulation remains bound to albumin via the acid-sensitive linker, and little free doxorubicin is released in the bloodstream.
- Doxorubicinol, which has been implicated in the pathogenesis of cardiomyopathy associated with doxorubicin treatment, can be detected only in trace amounts. The negligible quantities of this molecule in the circulation may account for the lack of cardiotoxicity observed thus far with aldoxorubicin treatment.
- In a first-line STS study, aldoxorubicin significantly increased PFS, PFS at 6 months and ORR compared to doxorubicin, as well as improved OS.

Clinical Studies Used in Safety Evaluation

1. An Open-Label Phase 1 Study to Investigate the Safety and Maximum Tolerated Dose of INNO-206 (Doxorubicin-6-Maleimidocaproyl hydrazone; DOXO-EMCH) Administered as a 30 Minute Infusion Every 3 Weeks in Subjects with Advanced Solid Tumors (INNO-206-P1-MTD-01)
2. An Open-Label Phase 1b Study to Investigate the Safety and Maximum Tolerated Dose of Aldoxorubicin (INNO-206) Plus Doxorubicin HCl Administered as Infusions Every 3 Weeks in Subjects with Advanced Solid Tumors (ALDOXORUBICIN-P1-MTD-02)
3. An Open-Label Phase 1 Study to Investigate the Pharmacokinetics of Aldoxorubicin (INNO-206; DOXO-EMCH) Administered as a 30 Minute Infusion Every 3 Weeks in Subjects with Advanced Solid Tumors (ALDOXORUBICIN-P1-PK-01)
4. A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma (INNO-206-P2-STS-01)
5. An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of Aldoxorubicin in HIV-Infected Patients with Kaposi's Sarcoma (ALDOXORUBICIN-P2-KS-01)
6. An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide (ALDOXORUBICIN-P2-GBM-01)
7. A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy (ALDOXORUBICIN-P3-STS-01)

Aldoxorubicin Exposure and Doxorubicin Equivalents

Clinical Study*	Aldoxorubicin median; mg/m^2 (range)	Doxorubicin Equivalents median; mg/m^2 (range)
[1]INNO-206-P1-MTD-01 (23 patients)	1,400 (350-2,800)	1,040 (260-2,080)
[2]ALDOXORUBICIN-P1-MTD-02 (16 patients)	1,200 (350-1920)	891 (260-1426)
[3]ALDOXORUBICIN-P1-PK-01 (15 patients)	1,050 (350-4,830)	780 (260-3,588)
[4]INNO-206-P2-STS-01 (75 patients)	2,100 (350-2,800)	1,560 (260-2080)
[5]ALDOXORUBICIN-P2-KS-01** (7 patients)	600 (150-900)	446 (111-669)
[6]ALDOXORUBICIN-P2-GBM-01** (9 patients)	1,750 (700-2,500)	1,300 (520-1,857)
[7]ALDOXORUBICIN-P3-STS-01** (55 patients)	1,400 (350-5,250)	1,040 (260-3,900)

*Patient number refers to those that received at least 1 dose of aldoxorubicin and 1 post-dose ECHO/MUGA. Superscript numbers refer to the studies listed under "Clinical Studies Used in Safety Evaluation". **Ongoing studies. Data taken as of 28Apr15.

Cardiac Evaluation Across Studies

% subjects with ≥10% decrease in LVEF:	16
% subjects with ≥10% increase in LVEF:	16
% subjects with <50% of expected value:	3
% subjects with QTc > 500 msec*	2.6

*Only includes the following studies where QTc was collected (see Clinical Studies Used in Safety Evaluation for study titles): 1, 2, 3, 5, 6, and 7.

Cumulative Doses of Aldoxorubicin and CHF

Number of Patients Received Aldoxorubicin	Cumulative Dose of Aldoxorubicin (mg/m^2)	Cumulative Doxorubicin Equivalents (mg/m^2)	Expected Historical CHF* (%) Based on Doxorubicin[4,5,6]	Observed CHF (%) in Aldoxorubicin Clinical Trials
55	≤ 800	≤ 580	< 7	0
37	801-1500	581-1087	18-50	0
107	≥ 1501	≥ 1088	> 50	0

*Congestive Heart Failure

Cardiac Safety Parameters from P2 STS Study*

% Subjects with ≥10% Decrease in LVEF from Baseline (n)**

CYCLE	Aldoxorubicin	Doxorubicin
2	4.7 (64)	7.7 (26)
4	7.8 (51)	35.0 (20)
6	5.3 (38)	18.2 (11)
End of Treatment	2.0 (51)	16.0 (25)
2 Mo Post End of Tx	3.7 (27)	33.3 (9)
5 Mo Post End of Tx	0 (16)	33.3 (3)
8 Mo Post End of Tx	10 (10)	0 (2)
11 Mo Post End of Tx	0 (7)	0 (0)
Any Cycle	12.2 (64)	29.4 (26)
% Subjects with LVEF < 50% of Expected	0	8.6

*See study #4 under Clinical Studies Used in Safety Evaluation.
**Number of subjects that had an ECHO or MUGA at that time point.

Troponin Results from P2 STS Study*

Median Troponin (ng/mL)

CYCLE	Aldoxorubicin	Doxorubicin
Baseline	0.01	0.01
2	0.01	0.01
4	0.01	0.02
6	0.01	0.08
End of Treatment	0.01	0.06
2 Mo Post End of Tx	0.01	0.02
5 Mon Post End of Tx	0.01	0.01

*See study #4 under Clinical Studies Used in Safety Evaluation.

PFS Results from P2 STS Study*

PFS	All Subjects Intent-to-treat	P Value
Aldoxorubicin	8.4 months	P=0.0004
Doxorubicin	4.7 months	
Improvement over dox	3.7 mos. (79%)	
Hazard ratio	0.419 (0.25-0.69)	P=0.0007
PFS at 6 Months		
Aldoxorubicin	45.7%	P=0.02
Doxorubicin	22.9%	
Improvement over dox	99.6%	

*See study #4 under Clinical Studies Used in Safety Evaluation

Serious Adverse Events Related to Aldoxorubicin*

- Febrile neutropenia (27 subjects; 11.5%)
- Anemia (6 subjects; 2.6%)
- Thrombocytopenia (6 subjects; 2.6%)
- Neutropenia (5 subjects; 2.1%)
- Vomiting (5 subjects; 2.1%)
- All adverse events seen with aldoxorubicin have been observed with other anthracycline treatments

*All studies listed under Clinical Studies Used in Safety Evaluation included.

Conclusions

- Aldoxorubicin can be safely administered at cumulative doses of over 2 g/m^2 without evidence of clinically significant cardiotoxicity.
- In 200 patients evaluated for cardiac safety, the median (range) exposure to aldoxorubicin was 1,750 mg/m^2 (150-5,250). The doxorubicin equivalents were a median of 1,300 mg/m^2 (111-3,900).
- Historically, the risk of CHF for doxorubicin increased if cumulative dose exceeded 500 mg/m^2; the risk exceeds 50% when the cumulative dose exceeds 800-1000 mg/m^2.[4,5,6]
- Based on the above data, FDA has removed the number of aldoxorubicin cycles and cumulative dose limit as long as it is of clinical benefit for anti-tumor response.
- Doxorubicin was associated with greater negative effects on cardiac function than aldoxorubicin.
- Aldoxorubicin could potentially be combined with other anti-tumor drugs without additional cardiac toxicity, such as trastuzumab in breast cancer.
- In a head-to-head comparison, aldoxorubicin was more effective in the treatment of STS than doxorubicin.
- This new anthracycline appears to lack clinical cardiac toxicity and could be the super doxorubicin of the future.

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