A Phase 1b/2 Study of Aldoxorubicin + Ifosfamide/Mesna in Untreated Sarcoma Patients

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Abstract

Objective: Aldoxorubicin (Aldox) is the albumin binding pro-drug of doxorubicin (Doxo) that releases Doxo under acidic conditions. In a phase 2b study, Aldox showed superior antitumor activity in first line soft tissue sarcoma (STS) compared to Doxo. No cumulative cardiac toxicity in Aldox arm reported. Ifosfamide (Ifos) has a long history of activity in sarcomas, alone or in combination with Doxo. Ifos is usually given as a 4-5 days infusion and is associated with significant toxicity. Continuous infusion (CI) of Ifos over 14 days is better tolerated and shown to be less neurotoxic and nephrotoxic. In this study the safety (MTD) and preliminary activity of Ifos + Aldox is being evaluated in sarcoma pts who had not received prior chemotherapy.
Methods: Escalating doses of Aldox were 170, 250 or 350 mg/m^2(equivalent to 125, 185 or 260 mg/m^{2}of Doxo) iv on Day 1 every 4 weeks. Ifos + mesna (1 gm/m^2/day each) are administered by CI for up to 14 days via a portable pump q4 weeks. Escalating doses of Aldox were administered if <2 of 3 or <3 of 6 patients who experienced a dose limiting toxicity during either cycle 1 or 2. Subjects were evaluated for AEs, treatment tolerability, labs, EKG, echo or MUGAs frequently, and CT scans to monitor tumor response by RECIST 1.1 every 8 weeks.
Results: From Sept 2014, 11 pts have been enrolled, seven in the 170 mg/m^2 cohort and 4 in the 250 mg/m^2 cohort. Based on DLTs observed in the 170 mg/m^2 and 250 mg/m^2 cohorts, the 350-mg/m^{2}cohort was not tested. Mean age 40 yrs (21-62 yrs), 8 pts had metastatic and 3 locally advanced disease. Nine pts are evaluable for response of which 2 pts had PRs, 5 pts have ongoing stable disease and 2 pts had progressive disease. Median number of cycles received thus far are 4 (range 2-5). Six/11 pts are still receiving treatment. Response assessment is ongoing and the median PFS has not been reached yet (range 2-9+ months). Most pts tolerated the treatment well. Main toxicity observed was Grade 3-4 neutropenia seen in 55% of pts but none required hospitalization or treatment discontinuation. No significant cardiac toxicity reported. In this ongoing study, pts will be treated at the 250-mg/m^2 dose level of in specific cohorts of leiomyosarcoma, liposarcoma, synovial sarcomas and unclassified pleomorphic sarcomas.
Conclusion: Combination of Aldox with Ifos given over 14 days infusion has shown to be feasible, safe, and has a favorable side effect profile. This combination indicates promising clinical activity and is being further explored.

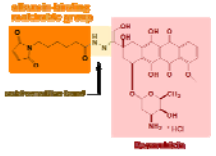
Background

- Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months after treatment with single agent doxorubicin.
- Doxorubicin, either alone or in combination with ifosfamide, is still considered the mainstay chemotherapeutic agent for the treatment of advanced, unresectable tumors.
- Aldoxorubicin in combination with a less toxic schedule for administering ifosfamide[1] may improve the activity of this combination without increasing its toxicity as has been demonstrated for ifosfamide as a single agent.

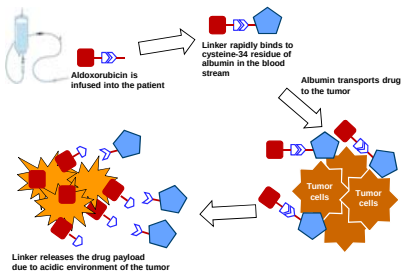
Aldoxorubicin

- 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.[2]
- Toxicological studies in mice, rats, and dogs demonstrated a 3- to 5-fold increase in the MTD, moderate and reversible myelosuppression, no liver toxicity and immunotoxicity, and no new toxicity compared to doxorubicin.[3]
- Aldoxorubicin is significantly less cardiotoxic in a chronic rat model when compared to doxorubicin at an equitoxic dose.[4]
- In a first-line STS study, aldoxorubicin significantly increased PFS, PFS at 6 months and ORR compared to doxorubicin.[5]
- Cumulative doses of 2000 mg/m^2 of doxorubicin equivalents have been achieved, which is over 3½ times the peak cumulative dose of standard doxorubicin.
- No clinically significant cardiac toxicities have been observed in clinical trials to date.

Structure of Aldoxorubicin



Proposed Mechanism of Action



Objectives

Primary

- To determine the preliminary safety of administration of aldoxorubicin in combination with ifosfamide/mesna in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma.

Secondary

- To evaluate the overall response rate, PFS, and PFS at 4 and 6 months.

Study Design

- Aldoxorubicin administered at either 170 or 250 mg/m^2 (125 and 185 mg/m^2 doxorubicin equivalents) intravenously (IV) on Day 1 every 28 days plus 1 gm/m^2/day ifosfamide and equal doses of Mesna by continuous intravenous infusion for up to 10-14 days (based on tolerability) via a portable/ambulatory infusion pump using a central line such as port-a-cath or PICC line.
- A subsequent dose level was to be administered if <2 of 3 or <3 of 6 subjects experienced a dose limiting toxicity during Cycles 1 and 2.
- Subjects with response (CR, PR, or SD) to initial combination therapy may continue with aldoxorubicin alone every 21 days at the same dose as used with the combination until disease progression, unacceptable toxicity or withdrawal of consent.
- Tumor response was monitored every 8 weeks using the RECIST 1.1 criteria.
- Safety assessments including adverse events, physical exam, serum chemistry, CBC, urinalysis, and ECG were performed at each visit.
- Cardiac function was assessed using either MUGA or cardiac ultrasound.
- Responses defined using RECIST 1.1 Criteria.

Key Eligibility Criteria

- Age between 15 and 80 years, male or female.
- Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma (including rhabdomyosarcoma, Ewing's sarcoma and mixed mesodermal sarcoma), chondrosarcoma or osteosarcoma of intermediate or high grade and gastrointestinal stromal tumors (GIST) (only in subjects that have progressed after receiving treatment with imatinib and sunitinib).
- Adjuvant or neoadjuvant chemotherapy (including doxorubicin) allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
- ECOG performance status 0-2.
- Life expectancy >12 weeks.

Patient Characteristics*

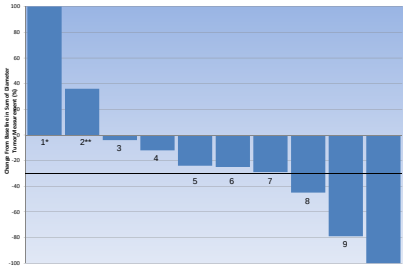
Characteristics	170 mg/m^2	250 mg/m^2	Total
N	7	3	10
Median Age, y (range)	42 (21-63)	42 (35-56)	42 (21-63)
Male / Female (#; %)	5 (71) / 2 (29)	2 (67) / 1 (33)	7 (70) / 3 (30)
Race (#; %)			
Caucasian	6 (86)	3 (100)	9 (90)
Black or African American	1 (14)	0 (0)	1 (10)
Asian	0 (0)	0 (0)	0 (0)
ECOG (#; %)			
0	0 (0)	0 (0)	0 (0)
1	7 (100)	3 (100)	10 (100)
Completed Aldox + Ifex Cycles (median; range)	5 (2-6)	4 (2-4)	4 (2-6)
Cumulative Aldox Dose (mg/m^2) (median; range)	850 (340-1000)	1000 (500-1000)	850 (340-1000)
Cumulative Dox equivalents (mg/m^2) (median; range)	631 (253-758)	743 (371-743)	631 (253-758)
*as of 15Sept2015			

Results

Best Response	170 mg/m^2 (%)	250 mg/m^2 (%)*
Complete Response	0 (0)	0 (0)
Partial Response	2 (28.6)	1 (50.0)
Stable Disease	4 (57.1)	1 (50.0)
Progressive Disease	1 (14.3)	0 (0)

*only 2 subjects have had a scan post-treatment as of 15Sept2015. The third subject in this cohort has not had a post-treatment scan as of this date.

Waterfall Plot – Target Lesion Response



*Large left thigh mass – refractory to chemotherapy
**Large right thigh mass – had significant reduction of pain, decrease SUV activity on PET scan

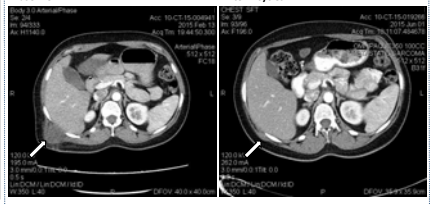
1. High grade pleomorphic sarcoma	6. Dedifferentiated chondrosarcoma
2. Rhabdomyosarcoma	7. Leiomyosarcoma
3. Dedifferentiated liposarcoma	8. Ewing sarcoma extraskeletal
4. Monophasic synovial sarcoma	9. Myxoid malignant fibrious histiocytoma
5. Osteosarcoma	10. Rhabdomyosarcoma

Representative CT Scans

50% Tumor reduction following 4 cycles of aldoxorubicin + ifosfamide (Subject 01-010)

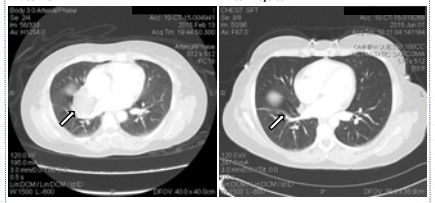
Abdominal/Chest Wall Mass

Baseline **After 4 cycles**



Right Infrahilar Mass

Baseline **After 4 cycles**



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Grade 3/4 Treatment Emergent Adverse Events (regardless of relationship)

	170 mg/m^2		250 mg/m^2	
	No. (%)		No. (%)	
Event	**Gr. 3**	**Gr. 4**	**Gr. 3**	**Gr. 4**
Neutropenia	2 (29)	4 (57)		3 (100)
Anemia	4 (57)		2 (67)	1 (33)
Sepsis	1 (14)			
Thrombocytopenia				1 (33)
Febrile neutropenia				1 (33)
Leucopenia			1 (33)	
Nausea/vomiting			1 (33)	
Hypoalbuminemia			1 (33)	
Epistaxis			1 (33)	
N=7 (170 mg/m^2); N=3 (250 mg/m^2)				

Cardiac Evaluation

- No clinically significant cardiotoxicity has been observed.
- No patients had clinically significant decrease in LVEF or QTc prolongation.
- No patients had clinical congestive heart failure.

Serious Adverse Events

- SAEs included febrile neutropenia (1) and sepsis (1).
- No treatment-related deaths occurred.

Conclusions

- Aldoxorubicin can be administered safely with continuous infusion of ifosfamide/mesna.
- No DLTs were observed in either cohort.
- 170 mg/m^2 cohort expanded to gain additional safety information.
- Treatment is associated with objective responses and stable disease.
- Common Grade 3 and 4 AEs were neutropenia and anemia.
- The median cumulative dose of aldoxorubicin is 850 mg/m^2 (doxorubicin equivalents 631 mg/m^2).
- **No significant cardiac problems were observed despite administration of median cumulative dose of doxorubicin equivalents of 631 mg/m^2.**
- Based on experience gained in this study, the decision was made to stop further aldoxorubicin dose escalation and continue to enroll the 250 mg/m^2 cohort.

References

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