A phase 1/2 study of aldoxorubicin and 14 days continuous infusion of ifosfamide/Mesna in metastatic or locally advanced sarcomas

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Abstract

Background: Aldoxorubicin (A) has demonstrated superior anti-tumor efficacy and lack of cumulative cardiac toxicity in multiple studies. A is doxorubicin (D) with a linker which rapidly binds in vivo to albumin after iv. We studied the combination of A administered on Day 1 with continuous infusion (CI) of ifosfamide/Mesna (I-M) days 1-14, as first line therapy or second line therapy in patients with sarcomas to evaluate efficacy and toxicity. **Methods:** 37 patients entered the study at one of 2 dose levels of A:170 or 250 mg/m2 (125 or 185 mg/m2 D equiv) administered on Day 1. I-M (1 g/m2 of each per day) was given up to 14 days as a CI via an out-patient portable pump. Chemotherapy cycles were repeated at 28 day interval. I-M was limited to a maximum of 6 cycles to avoid cumulative marrow toxicity, but A was continued in responding patients for clinical benefit. Subjects were followed for tumor response by CT scans and echocardiogram for cardiac toxicity every 8 weeks along with standard labs. **Results:** Of the 37 patients enrolled as of June 16, 2016, the results of 24 evaluable patients are presented here. Twenty of the 24 patients had soft tissue sarcoma, 2 had metastatic osteosarcoma and 2 had dedifferentiated chondrosarcoma. Eight of 24 patients (33%) had a partial response (PR), 15/24 (62%) had stable disease (SD) and only 1/24 (5%) had progressive disease with over all disease control rate of 95% (PR+SD). Eleven of 24 (46%) patients had received at least 6 cycles of A (cumulative D equivalent more than 1000 mg/m2). Four patients were considered surgically resectable after 6 cycles of chemotherapy with percent of tumor necrosis of 95% and 90% in one patient each and 80% in two patients. Median duration of PFS was 6+ (2-19+) months. The most prevalent toxicity was gr 3 or 4 neutropenia. Three patients had SAEs of febrile neutropenia. There was no clinical cardiac toxicity/ congestive heart failure. No patient had LVEF < 50% on echocardiograms at any time. **Conclusions:** The combination of A + I-M appears to be superior in anti-tumor efficacy to D/I-M with durable responses. A + I-M combination is quite tolerable with expected reversible hematologic toxicity. Of the 46% patients who received more than 1000 mg /m2 of D equivalent; no cardiac toxicity was observed.

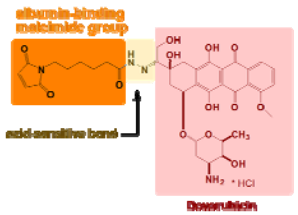
Background

- 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.
- In a phase 3 trial (EORTC 32012), discontinuation of treatment due to toxicity was 6 times greater in patients treated with doxorubicin and ifosfamide compared to patients receiving single-agent doxorubicin.

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



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.

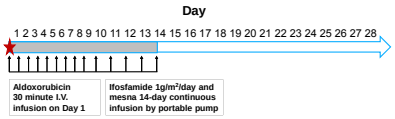
Secondary

- 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.

Treatment Schema: 28-Day Cycle



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
N	7	31
Median Age, y (range)	42 (22-63)	55 (19-76)
Male / Female, # (%)	5 (71) / 2 (29)	20 (65) / 11 (35)
Race, # (%)		
Caucasian	6 (86)	27 (87)
Black or African American	1 (14)	1 (3)
Asian	0 (0)	2 (6)
American Indian or Alaska native	0 (0)	1 (3)
ECOG, # (%)		
0	0 (0)	0 (0)
1	7 (100)	31 (100)
Prior Chemotherapy (≤ 2), n (%)	0 (0)	9 (29)
BSA (m^2), median (range)	2.0 (1.8-2.4)	1.9 (1.4-2.3)
Completed Aldoxorubicin Cycles, median (range)	5 (2-19)	3.5 (1-17)**
Completed Ifosfamide Cycles#, median (range)	5 (2-6)	3 (1-6)**
Cumulative Aldox Dose (mg), median (range)	1836 (748-6409)	1763 (475-6375)
Cumulative Dox equivalents (mg), median (range)	1364 (556-4761)	1309 (353-4736)

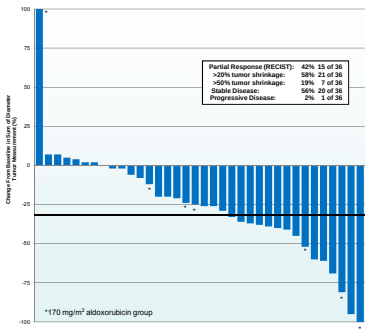
*as of 06Sep2016; #6 cycles were the maximum allowed; **several subjects just started the study

Results

Best Response	170 mg/m^2 (%) N=7	250 mg/m^2 (%)* N=29
Complete Response	0 (0)	0 (0)
Partial Response	2 (29)	12 (41)
Stable Disease	4 (57)	17 (29)
Progressive Disease	1 (14)	0 (0)

*29 subjects have had a scan post-treatment as of 06Sept2016.

Waterfall Plot – Best Target Lesion Response



Cardiac Evaluation

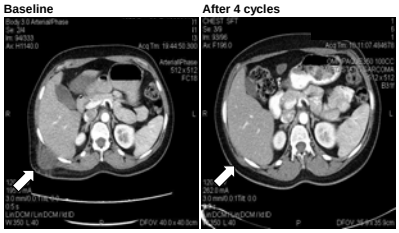
- No clinically significant cardiotoxicity has been observed.
- No patients had clinically significant decrease in LVEF or QTc prolongation.
- No patients had clinical congestive heart failure.

Representative CT Scans

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

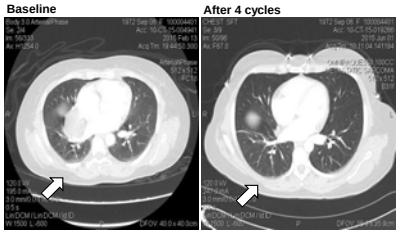
Abdominal/Chest Wall Mass

Baseline / After 4 cycles



Right Infrahilar Mass

Baseline / After 4 cycles



Grade 3/4 Treatment Emergent Adverse Events (related to either or both)

	170 mg/m^2		250 mg/m^2	
	No. (%)		No. (%)	
Event	**Gr. 3**	**Gr. 4**	**Gr. 3**	**Gr. 4**
Neutropenia	2 (29)	4 (57)	7 (26)	12 (44)
Anemia	4 (57)		13 (48)	2 (7)
Thrombocytopenia			3 (11)	3 (11)
Febrile neutropenia		1 (14)		4 (15)
Leucopenia			1 (4)	1 (4)
Nausea			2 (7)	
Vomiting			2 (7)	
Pyrexia				1 (4)
Bacteremia/sepsis	1 (14)			

As of 06Sep2016 data available; N=7 (170 mg/m^2); N=27 (250 mg/m^2)

Serious Adverse Events (related to either or both)

- SAEs included febrile neutropenia (5), thrombocytopenia (1), stomatitis (1), pyrexia (1) and anemia (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.
- Treatment was associated with a HIGH percentage of objective responses and stable disease.
- Common Grade 3 and 4 AEs were neutropenia and anemia.
- The median cumulative dose of aldoxorubicin for the 170 mg/m^2 cohort is 1836 mg/m^2 (range: 748-6409) (doxorubicin equivalents 1364 mg/m^2 [range: 556-4761]).
- The median cumulative dose of aldoxorubicin for the 250 mg/m^2 cohort is 1763 mg/m^2 (range: 475-6375) (doxorubicin equivalents 1309 mg/m^2 [range: 353-4736]).
- **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. mPFS has not been reached at this time.

References

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