Clinical Trial in Soft Tissue Sarcoma

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I. Introduction

Soft tissue sarcomas (STS) are a rare group of tumors of mesenchymal origin comprising about 1% of all malignancies in the adulthood.[1] Systemic therapies metastatic disease have been restricted for decades to very few effective and approved agents such as doxorubicin and Ifosfamide.[1]

Doxorubicin is an active agent in the treatment of advanced STS to produce meaningful response rates and remains a standard of first-line therapy. Two-drug combinations allow higher response rates, which is useful in patients with symptomatic disease or those in whom resection of limited metastatic disease is considered. [2] The combination of doxorubicin with a second active agent such as ifosfamide has been investigated on a number of occasions.[3] However, ifosfamide is characterized by a relevant incidence of neuro and nephrotoxicity with high doses.[1]

Hypoxic microenvironment arise in solid tumors due to the rapid cell , which contributes to the cancer progression.[4]

Evofosfamide is an investigational 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide designed to be selectively activated under hypoxic conditions.[5] It has been predicted that preferential metabolic activation of evofosfamide in the relative hypoxia of the tumour and would reduce systemic levels of toxic metabolites whilst enhancing efficacy relative to ifosfamide.[6]

The study aims to compare the efficacy and safety between the combination of evofosfamide and doxorubicin and Doxorubicin alone. The data utilized for this project came in three sets. The first set was baseline information. In this dataset, each subject had one observation which contained measurements of their demographic and health information that is relevant to the study. Also included were data about the best tumor response for each subject. During each follow-up, subjects had their change in tumors recorded. The results were categorized into the quality of response. The best tumor response data contained one observation for each subject, which was the most positive response for that subject from the study. The adverse event data was the third dataset utilized. This dataset contained multiple observations for each subject. If a subject experienced an adverse event, it was recorded sequentially, along with qualitative characteristics of the adverse event. The experiment was set as followed:

Criteria: Patients were aged 15 years or older with a diagnosis of an advanced unresectable or metastatic soft-tissue sarcoma of intermediate or high grade, for which no standard curative therapy was available, Eastern Cooperative Oncology Group performance statuses of 0-1, and measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1.[7]

Treatments: Patients were randomly assigned (1:1) to receive doxorubicin alone (75 mg/m2 via bolus injection administered over 5-20 min or continuous intravenous infusion for 6-96 h on day 1 of every 21-day cycle for up to six cycles) or doxorubicin (given via the same dose procedure) plus evofosfamide (300 mg/m2 intravenously for 30-60 min on days 1 and 8 of every 21-day cycle for up to six cycles). After six cycles of treatment, patients in the single-drug doxorubicin group were followed up expectantly whereas patients with stable or responsive disease in the combination group were allowed to continue with evofosfamide monotherapy until documented disease progression. [7]

Stratified Conditions: A web-based central randomization with block sizes of two and four was stratified by extent of diseases doxorubicin administration methods, and previous systemic therapy. [7]

Unblinded: Patients and investigators were not masked to treatment assignment. [7]

II. Results

1. Comparison on baseline values between the two groups

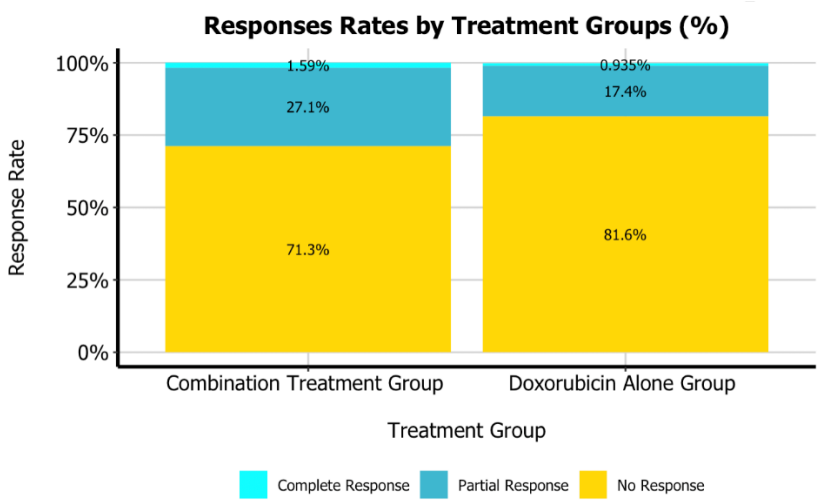
Here we present a table (Table 1) comparing the baseline information between study groups. Each of the traits at baseline is quite similar across groups. The fourth variable in the chart is HISTGRP, which stands for histological group. This is a descriptive classification of a tumor. BECOG is an inclusion criteria representing a patient's ability to withstand treatment. STAGE refers to the stage of cancer at the patients diagnosis. PRADL, PSURGFL, and PCHEMFL are flags for whether a patient has had prior radiotherapy, cancer-related surgery, or systemic therapy as a part of their treatment prior to the study. During exploratory hypothesis testing, each of the traits did not have a significant difference across study arms, except for stage. This led to a later analysis looking more closely at the results, stratified by age.

2. Difference in response rate between the two groups

Of the 640 patients in the best response analysis, 4 patients with the Eastern Cooperative Oncology Group performance (ECOG) status of 2 and 1 patient without the ECOG status were excluded. Based on the Response Evaluation Criteria in Solid Tumors version 1.1, 592 of 635 patients had been assigned to one of the following categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progression Disease (PD), and Inevaluable Responses (NE). Both CR and PR were regarded as objective responses in this study. Patients in the combination treatment group achieved a significantly greater proportion of response than patients in the doxorubicin alone group. (Figure 1) Specifically, 90 of 314 patients in the combination treatment group and 59 of 321 patients in the doxorubicin alone group achieved responses. (28.7% vs 18.4%; Chi-squared Test, $p = 0.00222$). Moreover, 8 of 635 patients were regarded as CR: 5 of 314 patients in the combination treatment group and 3 of 321 patients in the doxorubicin alone group (1.59 % vs 0.935%; Fisher's Test, $p = 0.501$). Further, 141 of 635

patients were regarded as PR: 85 of 314 in the combination treatment group and 56 of 321 in the doxorubicin alone group (27.1% vs 17.4%; Chi-squared Test, p = 0.00353).

Figure 1 Response Rates by Treatment Groups



3. Difference in adverse event profile between the two groups

There is a difference in the profile of adverse events between the combination treatment group and doxorubicin alone group. (Table 2) It appears as though there are a higher proportion of serious adverse events in the single-drug group (AESER Y: A 5.08%, B 5.74%). Participants who had combination drugs have a higher possibility to recover from adverse events (AEOUT RECOVERED/RESOLVED: A 71.83%, B 67.86%). According to the Common Terminology Criteria for Adverse Events from the National Cancer Institute (NCI CTCAE), the toxicity grade indicates the severity of adverse events. Specifically, grade 5 indicates death related to adverse events, and grade 1 indicates mild adverse events without interventions. It seems that participants in the single-drug group had more adverse events with high levels of toxicity grade.

There are 24 different system organ classes, but the top 10 constitute more than 90% of the total adverse event record size. It is proper to use these top 10 events to represent all system organ classes, and the rest 14 system organ classes have been classified to others. As the table presents, participants in group A are more likely to have merely three adverse events, including skin and subcutaneous tissue disorders, infections and infestations, musculoskeletal, and connective tissue disorders. From the analysis of the top 10 primary system organ classes, it appears as though doxorubicin plus evofosfamide can reduce the possibility of adverse events.

Table 1 Baseline Information

Traits	ArmA	ArmB
AGE		
Mean +- SD	57.4 +- 12.8	56.8 +- 13
Median (min, max)	60 (20, 89)	60 (20, 89)
SEX		
F	171 (54.46%)	172 (53.58%)
M	143 (45.54%)	149 (46.42%)
RACE		
AMERICAN INDIAN OR ALASKA NATIVE	0 (0%)	3 (0.93%)
ASIAN	5 (1.59%)	12 (3.74%)
BLACK OR AFRICAN AMERICAN	10 (3.18%)	15 (4.67%)
OTHER	4 (1.27%)	7 (2.18%)
WHITE	295 (93.95%)	284 (88.47%)
ETHNIC		
HISPANIC OR LATINO	18 (5.73%)	15 (4.67%)
NOT HISPANIC OR LATINO	296 (94.27%)	306 (95.33%)
HISTGRP		
EPITHELIOID	4 (1.27%)	8 (2.49%)
LEIOMYOSARCOMA	117 (37.26%)	113 (35.2%)
LIPOSARCOMA	61 (19.43%)	49 (15.26%)
MALIGNANT PERIPHERAL NERVE SHEATH TUMOR	7 (2.23%)	11 (3.43%)
MYXOFIBROSARCOMA	11 (3.5%)	14 (4.36%)
OTHER	78 (24.84%)	79 (24.61%)
PLEOMORPHIC RHABDOMYOSARCOMA	0 (0%)	4 (1.25%)
PLEOMORPHIC SARCOMA/MALIGNANT FIBROUS HISTIOCYTOMA	36 (11.46%)	43 (13.4%)
BECOG		
0	181 (57.64%)	184 (57.32%)
1	133 (42.36%)	137 (42.68%)
STAGE		
Stage I	8 (2.55%)	22 (6.85%)
Stage II	63 (20.06%)	73 (22.74%)
Stage III	143 (45.54%)	116 (36.14%)
Stage IV	95 (30.25%)	106 (33.02%)
NA	5 (1.59%)	4 (1.25%)
PRADFL		
Y	116 (36.94%)	118 (36.76%)
N	198 (63.06%)	203 (63.24%)
PSURGFL		
Y	314 (100%)	321 (100%)
PCHEMFL		
Y	20 (6.37%)	22 (6.85%)
N	294 (93.63%)	299 (93.15%)

Table 2 The Profile of Adverse Event

Traits	ArmA	ArmB
AESER		
Y	306 (5.08%)	196 (5.74%)
N	5718 (94.92%)	3220 (94.26%)
AEOUT		
FATAL	8 (0.13%)	3 (0.09%)
NOT RECOVERED/NOT RESOLVED	1412 (23.44%)	961 (28.13%)
RECOVERING/RESOLVING	247 (4.1%)	117 (3.43%)
RECOVERED/RESOLVED	4327 (71.83%)	2318 (67.86%)
UNKNOWN	6 (0.1%)	4 (0.12%)
NA	24 (0.4%)	13 (0.38%)
AETOXGR		
1	3397 (56.39%)	1836 (53.75%)
2	1663 (27.61%)	897 (26.26%)
3	749 (12.43%)	459 (13.44%)
4	207 (3.44%)	221 (6.47%)
5	8 (0.13%)	3 (0.09%)
AESOC		
Gastrointestinal disorders	1404 (23.31%)	896 (26.23%)
Blood and lymphatic system disorders	727 (12.07%)	428 (12.53%)
General disorders and administration site conditions	600 (9.96%)	413 (12.09%)
Skin and subcutaneous tissue disorders	697 (11.57%)	236 (6.91%)
Investigations	418 (6.94%)	316 (9.25%)
Metabolism and nutrition disorders	324 (5.38%)	206 (6.03%)
Respiratory, thoracic and mediastinal disorders	333 (5.53%)	194 (5.68%)
Infections and infestations	347 (5.76%)	128 (3.75%)
Nervous system disorders	286 (4.75%)	164 (4.8%)
Musculoskeletal and connective tissue disorders	264 (4.38%)	148 (4.33%)
Other	624 (10.36%)	287 (8.4%)

III. Conclusion

It appears that the baseline information for our two study arms is quite consistent. We have evidence that Arm A, which is our treatment group, had a higher proportion of subjects with a response to treatment than Arm B. By measuring the best tumor response during the study, the treatment appears to be more effective than control. The adverse event profile traits appeared mostly similar across study arms, but further investigations indicated that Arm A was more likely to have an adverse event in eight of the ten most frequent system organ classes. These results suggest that there may be additional adverse event risks in the treatment group. Additionally, it was found that, for some stages of cancer, the proportions of adverse events that were serious was less in Arm A than in Arm B. To conclude, Arm A performed better when measuring the best tumor response, but the results were mixed when considering the adverse event profile.

IV. References

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IV. Appendix

1. Comparison on severe adverse events between two groups stratified by stages

Prompted by the differences in stage found in the baseline information, we pursued an additional analysis of the proportions of adverse events that were serious, stratified by stage (Figure 2, Table 3). The null hypothesis for each stage is that the proportions of serious adverse events are the same across study arms. The alternative hypothesis for each stage is that the proportions of serious adverse events are different across study arms. The results are each considered with a significance level alpha = 0.05. Stages 1 and 3 had significantly different proportions of adverse events. Stages 2 and 4 did not have significantly different proportions of adverse events. Thus, we have evidence that for stages 1 and 3, the proportion of serious adverse events differs across study arms. In both stages 1 and 3, the proportion of serious adverse events is higher for Arm B. For stages 2 and 4, we do not have evidence that the proportions of adverse events differ across study arms.

2. Relative risk ratio for top 10 adverse events

We have done a further exploration by calculating the relative risk ratio for each top 10 adverse event system organ class. For example, according to the adverse event data, we can generate a contingency table for the adverse event system organ class Gastrointestinal Disorders (Table 4). 278 of 309 (90%) patients in Group A, and 256 of 306 (83.7%) patients in Group B have ever had adverse events related to this system organ class. (Table 5) According to table 3, by calculation, the relative risk ratio (incidence rate of adverse event related to gastrointestinal disorders in group A / incidence rate in group B) is 1.36, with 95% confidence interval 1.14 to 1.63, which means that subjects in group A are suffering from the risk 1.36 times as group B having the adverse event. As 1 is not included in the confidence interval, we can say that group A has significantly higher risk than group B to suffer from adverse events related to gastrointestinal disorders.

Similarly, the distribution of arms and adverse event status as well as the relative risk ratio with 95% CI is summarized as follows. 8 of 10 top adverse event system organ classes have a relative risk ratio significantly higher than 1, which means that patients treated by doxorubicin combined with evofosfamide have higher risk to have adverse events for most of the system organ classes.

3. Comparison on system organ classes and adverse event severity between age groups

According to the background research, there may be a difference in the distribution of adverse events between the young and middle-aged groups (age <= 60) and the elder group (age > 60). Stratified by arms, in terms of the number of adverse event system organ classes that a patient has ever had during the entire study as well as the distribution of patients whether they have had severe adverse events or not. (Table 6)

From this table, we have the following findings:1)For the number of adverse event system organ classes, there is a significant difference between the two age groups when alpha is 0.05 (p-value = 0.019) in the doxorubicin alone group, while the difference disappeared in the combined group; 2)For the number of patients that have ever had a severe adverse event during the whole study, there is a significant difference between the two age groups when the significance level equals 0.1 (p-value = 0.089). It seems as though the elder group is more likely to suffer from a severe adverse event than the young and middle-aged groups (5.4% vs. 1.9%).

Table 3 Adverse Events Stratified by the Stage

Traits	ArmA	ArmB	P
Stage I			
AESER			0.023
Y	7 (3.11%)	24 (8.16%)	
N	218 (96.89%)	270 (91.84%)	
Stage II			
AESER			0.57
Y	52 (4.18%)	31 (3.63%)	
N	1192 (95.82%)	822 (96.37%)	
Stage III			
AESER			0.042
Y	145 (5.32%)	80 (7.01%)	
N	2581 (94.68%)	1062 (92.99%)	
Stage IV			
AESER			1
Y	90 (5.25%)	57 (5.27%)	
N	1624 (94.75%)	1025 (94.73%)	

Figure 2. Adverce Events Stratified by the Stage

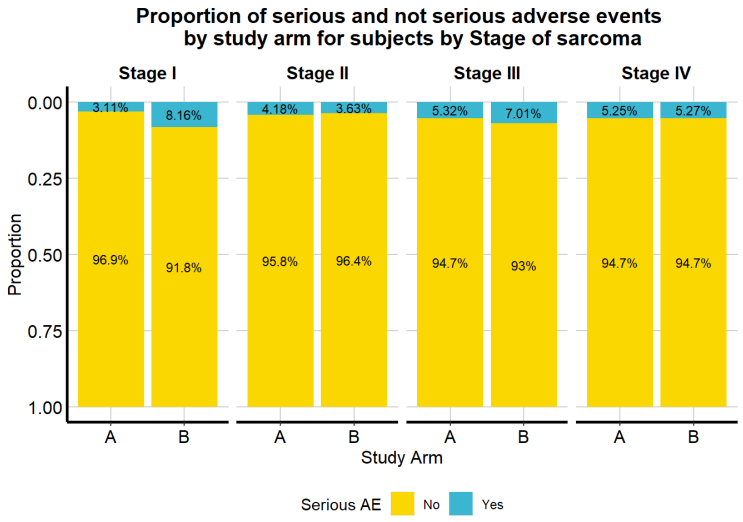

Table 4 An Example of Contingency table for Adverse Event

	Adverse Event	
Arm	Yes	No
A	278	256
B	31	50

Table 5 Point estimation of the Relative Risk Ratio and 95% CI for Top10 AESOC

Adverse Event System Organ Class	**ARM A (yes)**	**ARM A (no)**	**ARM B (yes)**	**ARM B (no)**	**Relative Risk Ratio (95%CI)**
Gastrointestinal disorders	278 (90%)	31 (10%)	256 (83.7%)	50 (16.3%)	1.36 (1.14,1.63)*
Blood and lymphatic system disorders	212 (68.6%)	97 (31.4%)	191 (62.4%)	115 (37.6%)	1.15 (0.98,1.35)
General disorders and administration site conditions	246 (79.6%)	63 (20.4%)	226 (73.9%)	80 (26.1%)	1.18 (1,1.4)
Skin and subcutaneous tissue disorders	236 (76.4%)	73 (23.6%)	164 (53.6%)	142 (46.4%)	1.74 (1.45,2.08)*
Investigations	158 (51.1%)	151 (48.9%)	121 (39.5%)	185 (60.5%)	1.26 (1.08,1.48)*
Metabolism and nutrition disorders	168 (54.4%)	141 (45.6%)	119 (38.9%)	187 (61.1%)	1.36 (1.16,1.6)*
Respiratory, thoracic and mediastinal disorders	164 (53.1%)	145 (46.9%)	119 (38.9%)	187 (61.1%)	1.33 (1.13,1.56)*
Infections and infestations	162 (52.4%)	147 (47.6%)	90 (29.4%)	216 (70.6%)	1.59 (1.35,1.86)*
Nervous system disorders	150 (48.5%)	159 (51.5%)	110 (35.9%)	196 (64.1%)	1.29 (1.1,1.51)*
Musculoskeletal and connective tissue disorders	137 (44.3%)	172 (55.7%)	101 (33%)	205 (67%)	1.26 (1.08,1.47)*

Table 6 Adverse Event Stratified by Ages

ARMCD		**<= 60 (N=339)**	**> 60 (N=276)**	**p value**
A	**Number of AESOC**			0.348
	1	5 (3.1%)	6 (4.1%)	
	2	5 (3.1%)	3 (2.0%)	
	3	17 (10.5%)	7 (4.8%)	
	4	17 (10.5%)	9 (6.1%)	
	5	13 (8.0%)	11 (7.5%)	
	6	18 (11.1%)	13 (8.8%)	
	7	25 (15.4%)	18 (12.2%)	
	8	19 (11.7%)	22 (15.0%)	
	9	20 (12.3%)	26 (17.7%)	
	10	14 (8.6%)	19 (12.9%)	
	11	9 (5.6%)	13 (8.8%)	
	Severe Adverse Event			0.089
	No	159 (98.1%)	139 (94.6%)	
	Yes	3 (1.9%)	8 (5.4%)	
B	**Number of AESOC**			0.019
	1	11 (6.2%)	1 (0.8%)	
	2	17 (9.6%)	5 (3.9%)	
	3	18 (10.2%)	19 (14.7%)	
	4	32 (18.1%)	13 (10.1%)	
	5	26 (14.7%)	27 (20.9%)	
	6	21 (11.9%)	14 (10.9%)	
	7	22 (12.4%)	17 (13.2%)	
	8	15 (8.5%)	15 (11.6%)	
	9	6 (3.4%)	12 (9.3%)	
	10	8 (4.5%)	6 (4.7%)	
	11	1 (0.6%)	0 (0.0%)	
	Severe Adverse Event			0.369
	No	170 (96.0%)	121 (93.8%)	
	Yes	7 (4.0%)	8 (6.2%)	