Factors Impacting the Establishment of Individual Soft Tissue Sarcoma Patient-Derived Orthotopic Xenografts (PDOX) Mouse Models: A UCLA Sarcoma Program Prospective Clinical Trial

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PDOX
Patient-Derived Orthotopic Xenografts

Objective

- Soft tissue sarcomas (STS) are among the most aggressive and chemotherapy-resistant neoplasms
- The surgical specimen providers a unique opportunity to obtain information to individual therapy when immortalized through a murine model
- Previous studies have been limited by small numbers, pre-clinical or laboratory settings, and subcutaneous tumor implantation
- The present study aimed to:
    1. Determine if we could develop STS patient-derived orthotopic xenograft (PDOX) models
    2. Identify clinical-pathologic factors associated with successful PDOX establishment

Methods

- Within a 1 year time period (5/2015–5/2016) all 107 patients who underwent resection of a biopsy-proven of potential STS were consented prior to surgery
- A sarcoma surgeon (FCE) obtained a portion of tumor in the operating room, which was transported fresh for surgical orthotopic implantation (SOI) in nude mice at PDOX Inc.
- The surgical orthotopic implantation (SOI) method has been previously described (1-4).
- Once a PDOX grew to 500 mm^3 and passaged it was considered established
- Mice without growth at 6 months were classified as a failed xenograft
- Given that no low grade STS PDOX established, only high grade PDOX were analyzed.

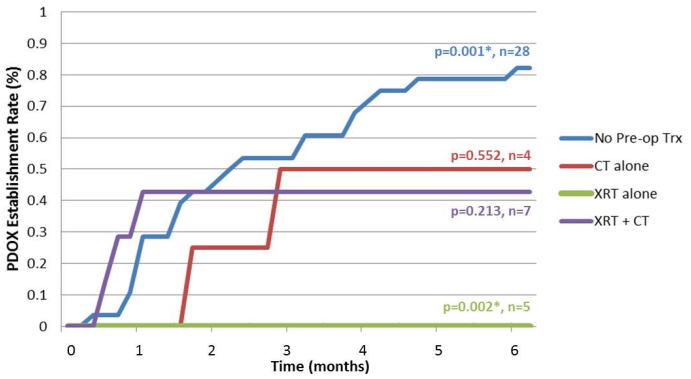
Results

- 107 STS underwent SOI, 71 high grade and 36 low grade
- Among the 71 high grade, 44 completed 6 month surveillance
- The overall take rate for high grade STS, to date, is 64% (28/44)
- Median interval for establishment was 46.5 days
- Take rates varied only by pre-operative therapy
- Untreated patients were 10.1 times more likely to successfully establish a PDOX as compared to pre-treated patients (p=0.002)
- Univariate & multivariate logistic regression demonstrated that only pre-operative radiation therapy significantly impacted the likelihood of PDOX establishment (OR 0.03, p=0.002).
- Pre-operative chemotherapy did not significantly diminish successful establishment (p-0.552)

	Sample n = 44		Take-Rate by Individual Factors		Univariate Logistic Regression		Multivariate Logistic Regression^	
	n	%	% (n)	p-value	OR (SE)	p-value	OR (SE)	p-value
Gender								
Female	23	52.27%	60.87% (14)		0.778 (0.490)	0.690		
Male	21	47.70%	66.67% (14)	0.690	Ref			
Grade								
Low grade	0	0.00%	0.00% (0)					
High grade	44	100.00%	63.64% (28)					
Presentation								
Primary	27	61.36%	62.69% (17)		0.927 (0.598)	0.907		
Recurrent or Metastatic	17	38.64%	64.71% (11)	0.907	Ref			
Location								
Trunk	22	50.00%	59.09% (13)		Ref			
Extremity	22	50.00%	68.18% (15)	0.531	1.484 (0.935)	0.532		
Subtype								
Leiomyosarcoma	9	20.45%	66.67% (6)	0.832	1.333 (1.176)	0.744		
Liposarcoma	9	20.45%	66.67% (6)	0.832	1.333 (1.176)	0.744		
NOS/Spindle Cell/UPS	11	25.00%	63.64% (7)	1.000	1.167 (0.955)	0.851		
Other	15	34.09%	60.00% (9)	0.718	Ref			
Neoadjuvant Chemotherapy								
Yes	11	25.00%	41.67% (5)		0.362 (0.259)	0.155	2.682 (2.797)	0.344
No	33	75.00%	45.10% (23)	0.830	Ref			
Neoadjuvant Radiation								
Yes	12	27.27%	25.00% (3)		0.093 (0.074)	0.003*	0.033 (0.038)	0.002
No	32	73.73%	78.13% (25)	0.001*	Ref			
Neoadjuvant Therapy								
None	28	63.64%	82.14% (23)	0.001*	10.120 (7.398)	0.002*		
Chemotherapy alone	4	9.09%	50.00% (2)	0.552	0.538 (0.567)	0.557		
Radiation alone	5	11.36%	0.00% (0)	0.002*	--	--		
Chemotherapy + Radiation	7	15.91%	42.86% (3)	0.213	0.360 (0.303)	0.224		
Xenograftability								
Success	28	63.64%						
Failure	16	36.36%						
	Median	Range						
Age	61	16 - 91			1.037 (0.022)	0.086	1.067 (0.030)	0.024
Size (cm)	7.15	0.9 - 35.5			0.971 (0.046)	0.536	1.007 (0.070)	0.925
Time to Establish (days)	46.5	9 - 184						

* significant at p<0.05
^ Multivariate logistic regression model included the following factors: age, size, neoadjuvant chemotherapy, neoadjuvant radiation. Pseduo R-squared 0.2971, likehood ratio chi squared 17.14 (p=0.0018)

Impact of Pre-Operative Therapy on PDOX Establishment



Conclusion

- This study demonstrates a very high (82%) establishment rate for PDOX in HG-STS patients who were treatment naïve at the time of surgical excision.
- Pre-operative/neoadjuvant radiation therapy significantly reduced the likelihood that a PDOX would establish; chemotherapy did not.
- In the largest PDOX study to date, we demonstrate that this is a feasible model for immortalizing individual patient HG-STS and potentially personalizing therapy.

References

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