Predicting Doxorubicin Response to Liposarcoma Using a Novel Genomic Matching Algorithm

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Abstract

Treatment for liposarcoma has not changed in over a decade. Doxorubicin remains a chief chemotherapeutic agent in its treatment but only a minority of patients respond. We propose a novel matching algorithm that takes advantage of available cell lines doxorubicin outcomes data (from the NCI-60) to predict whether or not patients will respond. We examined the gene expression profile of nineteen liposarcomas with known outcomes to doxorubicin. We matched their genomic profile to out the NCI-60 and based on the closeness of the cell line match, we predicted the consensus outcome. This algorithm correctly predicted liposarcoma outcome with a sensitivity of 87% and a specificity of 75%. This early work suggests this algorithm may be effective for predicting other drug outcomes in a simple unbiased manner.

Background

Metastatic liposarcoma is considered an incurable disease with few treatment options. Chemotherapy with doxorubicin remains a standard of care with only a minority of patients responding. To avoid toxicity in patients who are unlikely to respond, predictive algorithms are needed.

Genomic profiles may provide insight into the nature of the tumor and there is a great deal of preexisting, publically-available data of drug outcomes that have been tested in cell lines. Current approaches to doxorubicin prediction have been unsuccessful and based on machine learning techniques to develop a classifier. We hypothesized that a weighted similarity match between a patient's genomic profile and that of known cancer cell lines may allow us to determine which patients will respond to treatment.

Methods

Datasets used and transformation: Growth Inhibitory concentration data (GI50) was downloaded from NCI website. National Cancer Institute's 60 Cancer Cell lines (NCI-60) gene expression data (GSE32474)[1] and liposarcoma set (GSE12972) were downloaded from GEO on June 1, 2013. The gene expression from the GEO files were first converted into pathways via FAIME[2].

Matching Algorithm: Java programming language was used to implement algorithm depicted on **Figure 1.**

Scoring Results: The prediction mechanism was then tested by using a set of 19 liposarcoma patient tumor cell lines treated with doxorubicin taken from the GEO database. Liposarcoma responses were categorized as responders and non-responders. Our algorithm was also set to define two categories thus sensitivity and specificity could be calculated based on the numer of true positives and true negatives.

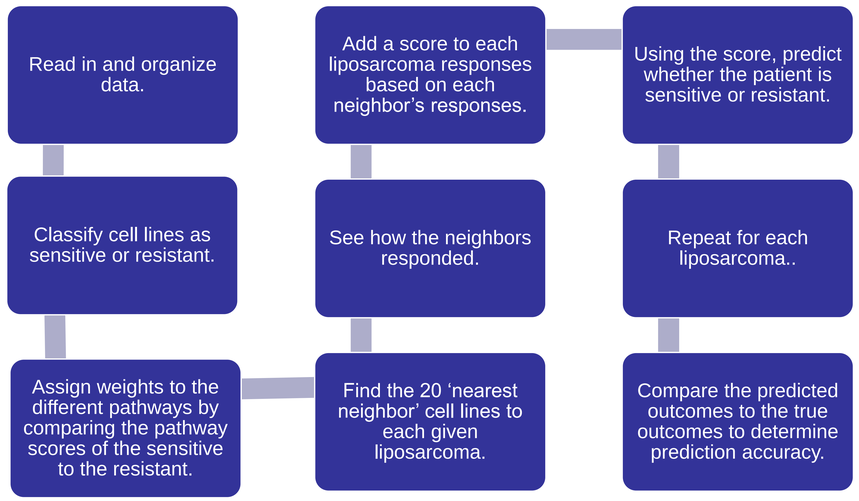

Figure 1: A flowchart visually representing the prediction algorithm

Results

We predicted the doxorubicin sensitivity for 19 patients with a sensitivity of 87% and specificity of 75% (Table 1) which was statistically significant with a p-value = 0.002 (binomial distribution).

Predicted	Observed Outcome		Total
	Sensitive	Resistant	
Sensitive	13 (TP)	2 (FP)	15
Resistant	1 (FN)	3 (TN)	4
	14	5	19

Table 1: A table showing prediction accuracy. Sensitivity is 87%, and specificity is 75%.

Discussion

A simple matching algorithm is able to classify difficult to predict chemotherapeutic sensitivities in liposarcoma. This methodology can be expanded to predict other types of chemotherapeutics or potentially for drug repurposing applications. Our results are limited by the small test set used and further research using other larger datasets will be necessary to validate our methods prior to clinical translation.

References

1. Daigeler et. Al. Heterogeneous in vitro effects of doxorubicin on gene expression in primary human liposarcoma cultures. Biomedical Cancer Center. 2008.
2. Yang et. al. Single Sample Expression Anchored Mechanisms Predict Survival in Head and Neck Cancer. PLOS Computation Biology. 2012.