DNA AND RNA PROFILES IN MACHINE LEARNING ALGORITHM TO PREDICT WHICH PATIENTS WITH AML/MDS WILL RESPOND TO VENETOCLAX-BASED THERAPY

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INTRODUCTION

Venetoclax in combination with hypomethylation agents is currently used as an alternative to standard induction therapy in patients with acute myeloid leukemia (AML) or advanced myelodysplastic syndrome (MDS). This is particularly relevant when patients are not eligible for standard induction therapy due to age or comorbidity. However, a little is known about which patient will benefit from such therapy and which patient will not respond. Selecting the right patient for such therapy is very important considering that these patients are clinically fragile to start with. Genomic profiling using DNA and RNA is becoming clinically a standard of care testing and there is a need to expand on the clinical utility of the generated data for this profiling.

AIM

Using RNA expression and DNA profiling of bone marrow cells from patients with MDS/AML generated by targeted transcriptome we explored the potential of developing an algorithm for the prediction of response to Venetoclax-based therapy. The machine learning algorithm is specifically designed to select and point out the specific genes that are relevant for prediction of response to venetoclax in myeloid neoplasms.

RESULTS

Of the 46 patients:

-Female : 18 (39%)

-Median age: 70.5 years (range 33-84). -- Most common mutations: ASXL1 ((41%), RUNX1 (26%), DNMT3A (24%), FLT3 (21%, NPM1 (20%), NRAS (20%), IDH1/2 (20%), TET2 (17%), TP53 (15%), and SRSF2 (11%).

-Complete Response (CR): 17 (37%)

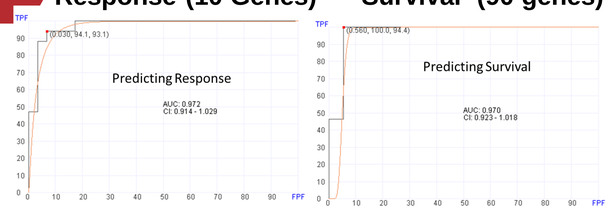
- Using machine learning and the expression of 10 genes, we were able to predict CR with AUC of 0.972 (95% CI: 0.914-1.00),

  Sensitivity: 94.1%; Specificity: 93.1%.

- Using machine learning algorithm and expression of 90 genes, we were able to predict overall survival with AUC of 0.970 (95% CI: 0.923-1.00)(Figure),

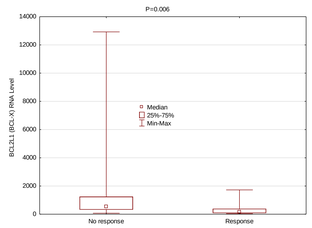
  sensitivity: 100% and specificity of 94.4%.

Response (10 Genes) **Survival (90 genes)**



TPF, true positive fraction (sensitivity); FPF, false positive fraction (specificity).

- TP53 was mutated in 7 patients, 6 of whom were non-responders, but no other statistically significant association between specific mutation and response.
- No significant difference between responders and non-responders in expression level of BCL2 (P=0.11), BAX (P=0.18) or MCL1 (P=0.54). BCL2L1 (BCL-XL) was significantly higher in non-responder (P=0.006)



10 genes predicted CR

Gene	Full Name	Function
EIF4A2	Eukaryotic Translation Initiation Factor 4A2	Involved in negative regulation of RNA-directed 5'-3' RNA polymerase activity
PLCG2	Phospholipase C Gamma 2	Catalyzes the conversion of IP3 and diacylglycerol (DAG). Both are important for transmitting signals from growth factor receptors and immune system receptors across the cell membrane.
Septin 5	Septin 5	Regulate cytoskeletal organization. Disruption of septin function disturbs cytokinesis.
CRTC1	CREB Regulated Transcription Coactivator 1	Enables cAMP response element binding protein binding activity. Involved in positive regulation of transcription by RNA polymerase II.
MAP2K5	Mitogen-Activated Protein Kinase Kinase 5	Interacts with and activates MAPK7/ERK5. The signal cascade mediated by this kinase is involved in growth factor stimulated cell proliferation and muscle cell differentiation.
MTOR	Mechanistic Target Of Rapamycin Kinase	Member of family of kinases that mediate cellular responses to stresses such as DNA damage and nutrient deprivation.
CDKN2D	Cyclin Dependent Kinase Inhibitor 2D	Member of the INK4 family of cyclin-dependent kinase inhibitors. This protein has been shown to form a stable complex with CDK4 or CDK6, and prevent the activation of the CDK kinases, thus function as a cell growth regulator that controls cell cycle G1 progression.
TAL1	TAL BHLH Transcription Factor 1, Erythroid Differentiation Factor	Involved in DNA-binding transcription factor activity; E-box binding activity; and histone deacetylase binding activity. Critical in myeloid cell differentiation; positive regulation of cellular component organization; and positive regulation of erythrocyte differentiation.
EPHB1	EPH Receptor B1	Mediate numerous developmental processes, particularly in the nervous system. Binds promiscuously transmembrane ephrin-B family ligands residing on adjacent cells, leading to contact-dependent bidirectional signaling into neighboring cells.
ACSBG1	Acyl-CoA Synthetase Bubblegum Family Member 1	Catalyzes the conversion of fatty acids such as long-chain and very long-chain fatty acids to their active form acyl-CoAs for both synthesis of cellular lipids, and degradation via beta-oxidation

METHOD

DNA and RNA from bone marrow samples from 46 patients with AML or advanced high-grade MDS treated with venetoclax (plus either azacitidine or decitabine) were sequenced using 177 gene DNA panel and 1408 gene RNA panel. We developed a machine learning algorithm that first selects the relative genes based on performance of each gene with cross-validation and based on stability measure using statistical significance tests. The selected genes were then used to predict response with k-fold cross-validation procedure (k=12). A naïve Bayesian classifier was constructed on the training of k-1 subsets and tested on the other testing subset.

CONCLUSIONS

This data shows that bone marrow expression profiling when used in a machine learning can provide valuable and practical approach for predicting response and overall survival to venetoclax-based therapy in patients with AML/MDS. This prediction requires complex data from large number of genes (10 to 90 genes) that must be incorporated in a machine learning algorithm. While farther studies are needed for confirmation, genomic profiling along with the machine learning algorithms can be a practical test for selecting specific therapeutic approach for the specific patient with AML/MDS.

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