Circulating Tumor DNA as a Prognostic Biomarker for CDK 4/6 Inhibitor Therapy in Metastatic Breast Cancer

Luis Chinea[1,2], Hannah L. Chang [1,2], and Isaac Chan [1,2,3]

1 Department of Internal Medicine, Division of Hematology and Oncology, 2 Harold C. Simmons Comprehensive Cancer Center, and 3 Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

UT Southwestern Medical Center

Background

Cyclin dependent kinase (CDK) 4/6 inhibition in addition with endocrine therapy (ET) is first line therapy for patients with hormone receptor-positive (HR+), HER2 non-amplified, metastatic breast cancer (mBC). Recognizing which patients are going to benefit from treatment and identifying which patients acquire resistance are still poorly understood. The advent of circulating tumor DNA (ctDNA) offers a unique noninvasive method to capture mBC heterogeneity. Studies have used ctDNA to monitor for emergence of mutations such as loss of function mutations to RB1. In this project, we test the hypothesis that ctDNA can be utilized as a biomarker to predict response to CDK 4/6 inhibitor therapy by identifying mutations and further characterizing the heterogeneity of these gene alterations.

Methods

In this study, we analyzed a subset of patients from the Dallas Metastatic Breast Cancer Study comprised of patients with HR+, HER2 non-amplified, mBC who underwent treatment with a CDK 4/6 inhibitor and ET in addition to ctDNA testing (n=102). Tempus xF and FoundationOne Liquid CDx liquid biopsy sequencing panels were utilized, which detects oncogenic drivers and resistance mutations. Mutations identified as The data was collected from a single academic medical center between the initial yea of ctDNA collection in 2019 to 2024.

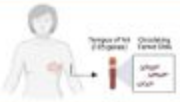

Figure 1 illustrates peripheral blood obtained from a breast cancer patient and analyzed using the Tempus xF panel to detect circulating tumor DNA.

Results

	Patients without Specified Mutations	Patients with Specified Mutations	Patients with RB1 Mutation
Total Patients	88	14	9
Gender			
Male	1 (1.2 %)	0	0
Female	87 (98.8%)	14 (100%)	9 (100%)
Age at Diagnosis			
Mean	55	54	53
AJCC Staging			
Metastatic (Stage IV)	88 (100%)	14 (100%)	9 (100%)
Non-Metastatic (Stage 0-IIIC)	0 (0%)	0 (0%)	0 (0%)
Type of CDK 4/6 Inhibitor			
Palbociclib	62 (70.4 %)	6 (42.9 %)	2 (28 %)
Ribociclib	9 (10.2 %)	1 (7.1 %)	0 (0%)
Abemaciclib	17 (19.4 %)	7 (50 %)	7 (72 %)

Table 1. Patient characteristics including: gender, age at breast cancer diagnosis, American Joint Committee on Cancer staging at time of ctDNA collection, and type of CDK 4/6 inhibitor treatment received. Specified mutations are CCNE1, MYC, and RB1.

	Patients without Specified Mutations	Patients with Specified Mutations	Patients with RB Mutation
Median Progression Free Survival (months) (mPFS)	13.5	7.5	7
Sites of Metastasis			
Bone	68 (77%)	11 (78%)	8 (89%)
Liver	33 (38%)	10 (71%)	5 (55%)
Lung	26 (29%)	4 28%)	2 (22%)
CNS	7 (8%)	2 (14%)	1 (11%)
Dermal	3 (3%)	0 (0%)	0 (0%)

Table 2. Median progression free survival of patients with designated mutations as tested with ctDNA. Genes of interest were CCNE1, MYC, and RB1. Among patients who did not have these gene alterations present, median progression-free survival (mPFS) was 13.5 months. Two patients had CCNE1 alterations mPFS was 5.5 months, three patients had MYC alterations mPFS was 19 months, and nine patients had RB1 alterations mPFS 7 months. Sites of metastasis within the three specified groups.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Acquired Mutation	RB1	RB1	RB1	RB1	MYC
AJCC Staging	Metastatic (Stage IV)				
Age at Diagnosis	43	35	50	46	62
Type of CDK 4/6 Inhibitor	Abemaciclib				Palbociclib
Duration of CDK 4/6 Inhibitor (months)	23	8	45	6	26
Location of Acquired Mutation	p.P28 (fs) p.V654 (fs)	p.R251 p.R787	p.R552	p.Q471	Copy Number Variant

Table 3. Shows individual characteristics of four patients that acquired a RB1 gene mutation and one patient that acquired a MYC mutation. Tempus xF or FoundationOne Liquid CDx liquid biopsy sequencing panels were utilized before CDK 4/6 inhibitor therapy was initiated and did not detect mutations in RB1 or MYC. Subsequent liquid biopsies after having progression on CDK 4/6 inhibitor therapy did reveal newly acquired mutations as specified above. Patient 1 had frameshift mutations and Patients 2-4 had loss of function point mutations in RB1. Patient 5 had a copy number variant mutation leading to copy number gain.

Conclusions

Researchers are actively seeking biomarkers that may predict favorable response and real time changes in tumor biology. This analysis further suggests patients undergoing treatment with CDK 4/6 inhibitor therapy may benefit from ctDNA analysis to evaluate for unfavorable gene alterations. The RB1 gene alteration occurred in approximately 9% of this patient population. Our study was limited by the small sample size and timing of ctDNA collection. Further studies are needed to provide insight on using ctDNA as a biomarker to track acquired tumor mutations that may indicate poor treatment outcomes.