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Short Communication

Retrospective Review of 374 Samples, Circulating DNA; As a Biomarker Assay to Support Clinical Management in Solid Tumors Treated with Multi Targeted Epigenetic Therapy (MTET)

Nezami M[1]*, Klowsowski C[2], Hager SJ[3]

[1]Research Cancer Institutes of America, Sahel Oncology, Newport Beach, California, USA; [2]Guardant Health, Genomic Specialist, Medical Affairs, Redwood City, California, USA; [3]California Cancer Associates for Research and Excellence, Fresno, California, USA

ABSTRACT

Here in this abstract we retrospectively review preliminary findings on 374 samples of circulating DNA extracted from 173 patients treated by multi targeted epigenetic therapy (MTET), which is a combination of natural histone deacetylase inhibitors and DNMT methyltransferase inhibitors. This therapy could dynamically interrupt the expression of altered genes, in a variety of solid tumor types, both in *in vitro* and *in vivo* models. We hypothesize that serial monitoring of the circulating DNA provides a feasible option for therapeutic decisions making based on presence of the driver genes in these cases. We also were able to track the antineoplastic response in these groups of patients by monitoring their tumor circulating DNA mutated allele fractions and propose a direct correlation with interim epigenetic therapy effectiveness.

Keywords: Epigenetics; Liquid biopsy; Circulating DNA

INTRODUCTION

Our current understanding of cancer biology and the epigenetic science has transformed our ability to deliver therapies more precisely to the genetic and epigenetic targets driving the tumor growth and disrupting its behavior. In concert with our efforts to regulate the transcription of altered genes involved in tumor biology, we have emphasized a range of epigenetically regulated driver genes that control the tumor key molecular targets, involved with its growth and metastasis [1]. Statistical analysis on epigenetically driven targets had shown improved outcome compared to historical control [2].

Unfortunately epigenetic targets are dynamically expressed [3] and no single drug can clinically be used to target the epigenome as drugs have static mechanism of action. This limiting factor has caused researchers in the field to admit their failure in development of an epigenetic formula or product that has significant clinical impact in majority of cancer types, mainly solid tumors. As a result, the effort on epigenetic drug development has shifted in recent years to hematological cancers, such as lymphomas and leukemia where these drugs can make a difference in the clinic [4-13].

We earlier had shown that a combination of histone and DNA selective demethylators used in a specific protocol was able to significantly produce meaningful results in our experimental therapeutic models. Although cytotoxic therapies and targeted drugs have been studied in the recent years to correlate with such relevance, using liquid biopsy in different types of cancer, including lung [14-16], lymphoma [17], renal cancer [18], breast cancer [19-21], colon cancer [22-26], ovarian cancer [27,28], this is to our knowledge the first time this correlation with epigenetic drugs have been explored.

MATERIALS AND METHODS

173 cases treated by MTET were collectively selected without selection bias. These cases were treated all in associated clinics of Medical centers of Hope.

The biomarker assays were performed through liquid biopsy through 374 samples. Amongst them 300 samples were positive for circulating DNA. 74 were negative. 66 patients had one sample and 63 patients had at least two samples (Tables 1 and 2).

Detection rate was 86 percent. The most and least common tumor types: 134 cases had breast cancer. 4 had glioblastoma. 20 cases carried BRCA alterations.

Correspondence to: M Nezami, Research Cancer Institutes of America, Sahel Oncology, Newport Beach, California, USA, E-mail: amnezami@yahoo.com

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In average 64 percent of such cases were stage four and had no other viable options left.

RESULTS

Serial monitoring of mutated allele fraction in circulating DNA analysis is feasible and clinically meaningful, when epigenetic drugs are applied in clinic and show positive clinical outcome based on such biomarker driven approach to epigenetic targets.

Table 1: 374 samples sent through the end of May 2018 on 173 patients. More than 1/2 patients in the practice (61%) have had serial testing (2 or more G360 tests).

Number of tests	Number of patients
1	66
2	63
3	17
4	13
5	9
6	2
7	2
8	1
Total	173

Table 2: Other and miscellaneous category.

Other/MISC	Count of cancer type
Anal Squamous Cell Carcinoma	2
Anaplastic Thyroid Carcinoma	1
Cancer, Other	2
Carcinoma of Unknown Primary (CUP)	7
Glioblastoma	3
Glioma	1
Neuroendocrine Carcinoma	1
Other	17
Other Squamous Cell Carcinoma	1
Thyroid Carcinoma	4
Grand Total	42

Table 3: Samples to date by cancer type, through end of April, 2019

Cancer Category	Count of samples
Bladder	7
Bone/Soft Tissue	14
Breast	186
Cervix	5
Endometrial/Uterine	11
GI	59
Head Neck	16
Kidney	7
Lung	34
Prostate	50
Miscellaneous/Other*	42
Ovarian	34
Skin	26
Grand Total	491

*Definitions on following slide

Table 4: FGFR4436 Common gene mutations breast cancer samples (genes identified 10 or more times in breast cancer samples to date).

Gene	Observed in data
Grand Total	644
PIK3CA	61
TP53	44
ERBB2	36
ESR1	32
NF1	32
EGFR	27
ARID1A	26
KIT	23
MYC	22
CCND1	21
BRCA1	20
BRCA2	20
FGFR1	20
MET	20
APC	18
RAF1	16
FGFR2	15
PDGFRA	14
BRAF	12
GATA3	12
CCNE1	11
CKD6	10
NOTCH1	10
ERBB2	36
CNV	14
SNV	22

4/22 SNVs: activating

Further analysis as of April of 2019, for 491 cases is currently on going and preliminary findings are consistent with this article with common genetic mutations reflected in breast cancer responding to the epigenetic therapies. (Tables 3 and 4).

CONCLUSION

We conclude that such biomarker based epigenetic approach in cancer therapy could replace the current standard of care which is mainly blind shot and type specific.

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