EDITORIAL

Liquid Biopsy: Opportunities and Expectations

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Introduction

Tumors have an abnormal rate of cell growth and cell division. Tumor cells release circulating tumor DNA (ctDNA), cell free DNA (cfDNA), mRNA and microRNA,[1] in the blood and body fluids which are the by-product of tumor cell lysis.[2] Both ctDNA and cfDNA provide valuable information regarding the cancer related mutations, genetic aberrations and presence of cell free Nucleic acid (cfNA).[3] The ctDNA provides information about the primary tumor and its secondaries / metastases. It is these ctDNA that anchor into novel locations and start dividing to develop secondaries of the tumours.[2]

Tumor biopsy is an invasive procedure in which tissue is excised from a growth and examined under a microscope. However, "Liquid Biopsy" is a relatively newer technique to find and evaluate cancer cells or their products in blood and body fluids that circulate after tumor cell lysis.

Historical Aspect for the Use of Liquid Biopsy:

The basis of liquid biopsy was the observation made by Ashworth[4] in 1869, where the circulating tumor cells were detected in a patient with tumor secondaries. The metastatic sites also shed tumor cells in the blood stream that could be detected and analyzed. It was after a long gap when scientists realized that the cell free DNA (cf DNA) could be detected, analyzed, and quantified. It was in 1948 when cell free DNA and free RNA was first detected and quantified.[5] This was done both in healthy individuals and those who had cancer. Progressing forward, it was in 1966 the researchers detected large volumes of cell free DNA in patients who had lupus. By 1980 the cell free DNA was also detected among oncology patients. In 1994 the scientists started detecting specific mutations from the cell free DNA present in the blood of oncology patients and by 2000 Veridex introduced CELL SEARCH® CTC test, for liquid biopsy assay as a first commercially available test for liquid biopsy, however CAPP Seq: cancer Personalized profiling by deep sequencing is another method for quantifying ctDNA analysis that is being used.[6] The Cobas® EGFR was the first liquid biopsy test that was approved by FDA in 2016. This test was for EGFR gene mutation to be detected in blood drawn from cancer patients.[7] Nowadays, ctDNA and cfDNA can be analyzed commercially by Mag Max Cell Free DNA Isolation kits and Cell Free Nucleic Acid Isolation Kits used for liquid biopsy specimens.[1]

Applications and Advantages of the Liquid Biopsy Technique:

When blood/body fluids are drawn as liquid biopsy for ctDNA and cfDNA, they also contain membrane bound lipid globules called Exosomes.[8,9] They contain tumor proteins, lipids, DNA fragments and micro RNA. The tumor related material in the exosomes can be analyzed to provide information about the mechanism involved in signals between the tumor cells, especially between primary tumors and metastatic sites. This is one of the many novel features of liquid biopsy and is not achieved by conventional tissue biopsy. Liquid biopsy provides a window of opportunity to understand tumor cell signaling that can be manipulated by various treatment modalities for cancer management. As cancer is a complex problem with systemic effects, liquid biopsy with frequent sampling provides a unique chance for mutation characterization and exosomal analysis.[10,11,12,13]

Together, these analytes have the strength to give the details of the tumors genetics, its metastasis and various stages of tumor progression.[14,15] The information provided is used for: genomics, epigenomics, transcriptomics, proteomics, metabolomics and information regarding minimal residual disease.[16] The major oncology domains where liquid biopsies have been successfully used are: colorectal,[17] breast and lung cancers, mainly to predict therapy responses and to monitor the

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patients for relapse. The developed assays are sensitive to detect these organ related mutations.[18,19]

Among other promising capabilities of liquid biopsy are the analysis of heterogeneity of tumor genetics, detection of very early treatment related resistance, detection of residual disease affecting prognosis, recurrence and follow up.[17,20,21,22]

Among the common applications for use of liquid biopsy technique is, early detection of cancer related DNA. This would help to plan the treatment, to review how well the patient is responding to treatment and to detect the recurrence of cancer. As liquid biopsy usually involves detection of cancer cells/DNA by drawing of blood, the same can be done multiple times. This helps the oncologists to monitor the molecular changes taking place in the tumor during treatment.[23] Liquid biopsies also provide a method to trace the tumor genetic variations sequentially that is not possible by using traditional tissue biopsy.[22]

Hence, liquid biopsy provides a non-invasive substitute for traditional tissue biopsies [25] and has become a popular field, with features for improved diagnoses for oncology and other types of diseases like Down Syndrome screening and detection of fetal DNA in maternal circulation.[2, 25, 26] Recently, liquid biopsy has made a place in Precision Medicine that manages patient with targeted therapies with improved detection of various genetic aberrations.[27]

Limitations of Liquid Biopsy Technique:

Despite many advantages there remain many challenges; from timing of sample, [28, 29] collection [30, 31] with relation to the stage of disease [32, 33, 34] adequate volume of sample collected, proper storage of sample, DNA isolation, sequencing and detection of relevant mutation, careful analysis with clinical validation of mutation analysis procedures.[35]

Summary and Conclusion:

It appears that the future of liquid biopsy is an ambitious endeavor and entails technological advancements but this procedure is gaining worldwide acceptance for early cancer detection, genetic evolution and monitoring of treatment resistance.[36] Moreover, with quantum leaps in technology and computation of data we can achieve much with the use of liquid biopsy and also save many precious lives through early revelation and analysis. [37,38,39,40]

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