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Liquid Biopsy When MEAT Is Not the TREAT

Cancer is a disease with the interplay of several genes. We endeavor to understand these genetic changes and treat it effectively. We have been improving our techniques in molecular biology towards this very goal. The role of tissue biopsy to establish the diagnosis is the cornerstone for initiating therapies.

Liquid biopsy is a new tool that has recently been added to the armamentarium of oncologists.

The whole society is abuzz with this "new" tool with articles appearing in newspapers and magazines. So, let us look at it in the right perceptive.

The NCI defines liquid biopsy as, "a test done on a sample of blood to look for cancer cells from a tumour that are circulating in blood or for pieces of DNA from tumour cells that are in the blood."[1]

It is a fact that as solid tumours grow beyond 1-2 mms, from being 'non-vascular' need to get 'vascular' for their growth and survival. This is accomplished by the process of "angiogenic switch," a process that we understand fairly well today. The neovasculature formed is leaky and permits tumor cells to enter circulation and thus aiding the process of metastasis. Furthermore, every day, a lot of other nucleic acids are shed into the bloodstream. It is estimated that each milliliter of blood contains 25 ng of cell-free DNA; thus, a tumor of 100 g sheds about 3.3% of tumor DNA daily. This is the basis for the concept of liquid biopsy.

At present, the concept of liquid biopsy has expanded to encompass studying circulating tumor cells (CTCs), DNA, RNA fragments, and exosomes from blood .The other sources of genetic material could be urine, saliva, sputum, cerebrospinal fluid, and bronchoalveolar lavage.

We understand the universal phenomenon of tumor heterogeneity, and this limits our knowledge of the whole tumor when studied on a tissue biopsy. The concept of liquid biopsy to a very large extent overcomes this drawback. It also permits serial, real-time acquisition of information due to the ease of access of genetic material, unlike a tissue biopsy.

The applications of the liquid biopsy are tremendous, from studying tumor biology and evolution, monitoring of treatment, assessing minimal residual disease, and detection of resistance and its mechanisms to screening and drug development.

Cristofanilli *et al*. studied CTCs in breast cancer and enumerating their numbers correlated with outcomes;[2] studies by Cohen in colorectal cancer[3] and de Bono in prostate cancer[4] showed similar findings. Zhang *et al*. published a meta-analysis of 49 studies with 6815 breast cancer patients and showed a correlation of the number of CTCs with progression-free survival and overall survival.[5] However, working with CTCs has a myriad of problems and hence many researchers have not pursued this path.

Circulating tumor DNA (ctDNA) is easier to work with and hence the efforts have progressed well with the same. Furthermore, the rapid fall in costing of genomic analysis has aided in extensive work in this field. Enormous data on several cancers have emerged from the Genome Atlas project. Several methods have been used to study the ctDNA including real-time polymerase chain reaction (PCR), digital droplet PCR, BEAMing, and next-generation sequencing (NGS). Each of these has its share of advantages and disadvantages. One needs to suit the platform depending on the need of the study. NGS is one of the most sensitive platforms for looking at several parameters in one go. All the platforms need adequate amounts of DNA, the lesser the quantity , one needs to use the most sensitive method.

A lot of work has been done on nonsmall cell lung cancer (NSCLC). In fact, it has become a well-accepted modality to look at resistance mechanisms in patients on tyrosine kinase inhibitors (TKIs). This is particularly significant in our populations where the epidermal growth factor receptor (EGFR) mutation rates are high as 35%.

Goto *et al*. have revealed that ctDNA could very well be used to study the EGFR mutations, and it has shown good correlation with outcomes with gefitinib comparable to the tissue-tested cohort.[6]

We are now able to look for the most common resistance mechanism, the T 790 M mutation, which occurs in 65%–70% of patients. Liquid biopsy is helpful in many of these patients as the tumor may be in difficult-to-access areas or the patients may not be medically fit for a transthoracic biopsy. We are now quite confident to treat patients with T790M with osimertinib when detected either in plasma or tissue as the outcomes have been shown to be identical.[7]

Studies are underway to quantitatively assess T790 M and use it as a biomarker to serially follow up patients.[8]

Carpenter *et al*., in a cohort of 102 NSCLC patients during a period of February 2015 to March 2016, showed that ctDNA analysis was helpful in detecting EGFR mutations in 86 samples and 56 of these patients had mutations that could be helped with potential off-label drugs.[9]

The role of ctDNA has been exploited in studying breast cancer as well. O'Leary at ASCO 2017 presented ctDNA

assessment to predict sensitivity to palbociclib and fulvestrant in breast cancer.

The SOLAR-1 study of P13K inhibitor in breast cancer evaluated P13K mutations in plasma and showed that it could be used as a biomarker to select patients for alpelisib.[10]

Recently, the researchers of Johns Hopkins University published results about their blood test "cancerSEEK". They looked for certain proteins in blood to prove the presence of cancer. Lichtenfeld, the Deputy Chief Medical Officer of the American Cancer Society, says that "cancer's early detection by means other than X-rays, colonoscopies, or Pap smears has been subject of research for at least 2 decades, now we have been learning about ctDNA to evaluate cancer and about pros and cons of trying to find cancer early."[11]

The benefits of early detection are several, but we have learned the lessons of lead-bias from conventional screening procedures. Furthermore, the lessons from detecting elevated PSA, we know that many people die with prostate cancer rather than because of it. Similar is the story of elevated CA-125. Thus as in screening, we have a lot to learn about the optimal use of liquid biopsy.

Venkatesan *et al*. in the ASCO 2016 Education Book have discussed tumor evolutionary principles and have shown the role of studying ctDNA for the same.

To conclude, the concept of liquid biopsy to study all the elements that can be obtained in the least invasive way throws open several opportunities to understand cancer better and thus helps our patients – after all, that is the objective of science and discovery.

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