Liquid Biopsy in Cancer Care – Improving Patient Outcomes and Reducing Healthcare Costs

Why are liquid biopsies becoming a popular form of testing in oncology drug trials, and what might their usage mean for patients?

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The use of liquid biopsy in oncology drug trials is rapidly expanding with continued anticipated growth.[1] This non-invasive, repeatable sampling technique can be easily implemented and has the potential to add great value to the clinical evaluation of new and existing therapeutics. In the clinic, liquid biopsy has the potential to support the advancement of personalised patient care pathways whilst improving patient experience and reducing subsequent healthcare costs.

Cancer is the leading cause of morbidity and mortality in most developed nations, responsible for an estimated 10 million deaths per year globally.[2] Most of us have been directly or indirectly affected by this disease, with Cancer Research UK estimating that one in two people will be diagnosed with cancer during their lifetime.[3] As such, improving cancer diagnosis and care are leading priorities in many healthcare systems, and services are continuing to evolve to progress cancer management and treatment. Effective and curative cancer treatment is continuously challenged by the heterogeneity of cancer on multiple fronts including:

- *Interpatient heterogeneity* – mutations vary from patient to patient, within the same cancer type
- *Intrapatient heterogeneity* – individual cancer patients having several different types of cancer cell mutations within a particular tumour
- *Clonal evolution* – individual cancer patients experiencing mutations and changes in their tumour(s) over time (as a result of treatment, disease progression or other factors).[4,5]

To treat patients effectively, clinicians require precise, actionable and up-to-date information in order to select the appropriate drug(s) to target an individual's cancer. In recent years, precision medicine, also known as personalised medicine, has been accepted worldwide as a promising way to improve patient outcomes. There is still a crucial need for actionable information on a patient's cancer status throughout the treatment pathway, which may span several years.

When cancer is first diagnosed, solid tissue obtained from a biopsy or resection of the primary tumour is currently considered the 'gold standard' sample needed for tumour characterisation. However, these are invasive procedures that are relatively costly, prone to adverse events and not suitable for repeat testing. In addition, solid tissue cannot always be obtained in difficult-to-access tumours, such as brain, pancreatic and lung cancers, or in situations where the patient is too unwell for the biopsy, surgery or both.

In contrast, liquid biopsies, where the cancer sample is provided from a blood test, are much less invasive, time-consuming and costly. The simplicity of obtaining a liquid biopsy sample makes it much easier for repeat sampling and analysis to be performed, allowing real-time monitoring of the patient's disease. The up-to-date information on a patient's cancer provided by a liquid biopsy could help to provide more effective and timely personalised treatment for patients.

What is a Liquid Biopsy?

A liquid biopsy enables the analysis and characterisation of cancers through biomarkers shed from tumours into a patient's bloodstream. These can be in the form of cells, DNA and RNA, proteins, enzymes, hormones, exosomes and more. Circulating tumour cells (CTCs), circulating tumour DNA (ctDNA) and exosomes from patient blood samples have gained

attention as useful biomarkers for investigating cancer status, heterogeneity, drug selection and response to treatment(s).

CTCs are live cancer cells released by the tumour into the bloodstream and are responsible for metastatic seeding. ctDNA is fragmented DNA released from dead or dying cancer cells into the bloodstream via a programmed and controlled pathway (apoptosis) or a non-controlled pathway (necrosis). Exosomes are membrane-bound extracellular vesicles that can contain a mixture of antigens, proteins, fragmented DNA, metabolites, lipids and other cellular material released from cancer cells.

A liquid biopsy offers access to all of these biomarkers, which could provide critical information on current disease status to be utilised in conjunction with standard of care guidelines for the creation of personalised treatment plans.[6] Liquid biopsies can be particularly useful for obtaining information in situations where tissue biopsy is not possible, for example, where surgery has already removed the main bulk of the tumour, where a particular tumour site is inaccessible, where there are multiple tumour sites and/or where the patient is too unwell to undergo a biopsy procedure.

Utility of Liquid Biopsies Throughout the Cancer Care Pathway

Cancer Diagnosis

Liquid biopsies are being investigated as a tool for screening populations of low-risk (asymptomatic) individuals, known as multi-cancer early detection tests (or MCEDs), and high-risk individuals where family history or symptoms indicate a risk of a particular cancer.[7]

Earlier cancer detection is a major focus for many national healthcare systems and could lead to greater treatment success and improved quality of life for patients. Similarly, CTCs and ctDNA have been shown to be useful as predictors of progression-free survival and overall survival.[6, 8]

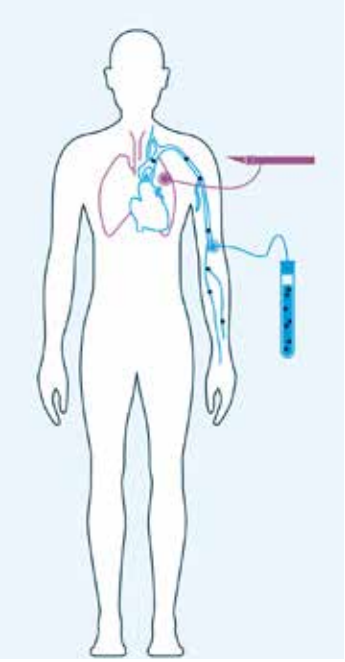

Figure 1:The differences between solid tissue and liquid biopsies

Interrogation of CTCs obtained from liquid biopsies can provide information on secondary metastatic lesions with different phenotypes and genotypes compared to the primary tumour, allowing tumour heterogeneity to be evaluated.[6, 8, 9]

Treatment Selection

CTCs and ctDNA can be subjected to downstream analysis for identification of prognostic markers and actionable clinical targets. These actionable targets (such as specific mutations) could help to guide the selection of more appropriate and personalised treatments.[4, 6, 9] The FDA has approved several liquid biopsy-based ctDNA assays for the detection of actionable mutations in solid tumours, for use as companion diagnostics matched to specific targeted cancer therapies.[4, 10, 11]

Treatment Monitoring

The use of liquid biopsies to predict and monitor a patient's response to therapy could help to avoid the use or continuation of ineffective treatments.[6, 8, 9]

Actionable targets within the tumour can change as the cancer is exposed to various therapies and mutates or evolves, and these targets have been shown to both mirror and diverge from the results obtained using the historical primary tumour tissue biopsy.[4, 6, 8, 9] The ongoing assessment of tumour status using liquid biopsies during treatment could provide real-time information on a patient's response to treatment and assess emerging heterogeneity, helping to guide treatment pathways that may tackle the development of resistance.[6, 8, 9]

Disease Progression and Relapse Monitoring

Liquid biopsies are simple and easy to implement as tools for the monitoring of patients post-treatment to help detect disease relapse and potentially guide the selection of the appropriate next stages of treatment.[4, 6, 8, 9]

Benefits of Liquid Biopsies in Clinical Trials

Liquid biopsies can be easily implemented and included in clinical trials, providing accessible, and a relatively inexpensive, alternative source of tumour material for interrogation,

addressing all areas of utility discussed above. All of the biomarkers available for assessment in a liquid biopsy (eg, CTCs, ctDNA, RNA, proteins, etc) can individually and collectively add great value to the evaluation of new and existing therapeutics. Liquid biopsy can also aid drug discovery, with many novel druggable targets identified in the literature.

The inclusion of liquid biopsy analysis in clinical trials could provide additional information to aid the selection of suitable study patient cohorts, leading to better treatment response and reduced likelihood of treatment failure.

In addition, a liquid biopsy could provide information quickly and inexpensively on how treatments and therapies are performing, allowing drugs to fail faster, rather than later during phase 3 and 4 clinical trials when significant investment has been made.

Currently, there are approximately 300 active, recruiting or not yet recruiting clinical trials utilising liquid biopsies on the clinicaltrials.gov registry. As an example, CTCs have recently been used in breast cancer clinical trials as a prognostic and predictive marker for risk stratification and treatment monitoring in patients, including the identification of HER2 positivity for targeted treatment selection.[12, 13] In a recent study of 105 advanced-stage breast cancer patients with HER2 negative tumours, patients with HER2 positive CTCs had improved progression-free survival after anti-HER2 targeted therapy whereas patients with HER2 negative CTCs derived no benefit.[14]

As such, the HER2 status of CTCs in late-stage breast cancer patients with HER2 negative primary tumours may help guide the use of anti-HER2-targeted therapy. Similarly, in prostate cancer, the CTC-derived androgen receptor splice variant 7 (AR-V7) has been assessed using liquid biopsy in clinical trials to evaluate prognosis and inform treatment response to androgen deprivation therapy in castration resistant prostate cancer.[15] This has led to the inclusion of CTC derived AR-V7 biomarker assessment in the National Comprehensive Cancer Network (NCCN) treatment guidelines for prostate cancer.[16]

Reduction of Healthcare Costs via Liquid Biopsies

Treatment of cancer patients can be very expensive. For example, a single chemotherapy drug can cost $10,000-100,000 for a course of treatment, depending on drug, method of administration and the number of treatments required.[17] Newer immunotherapy drugs can cost $100,000-200,000 for a course of treatment.[18]

Even though such drugs are prescribed as the most appropriate treatment option, typically less than 15% of immunotherapy patients will benefit and respond, with many patients experiencing cancer recurrence following an initial period of remission.[19]

In this situation, roughly 85% of the drug cost may be wasted on patients who will have limited benefit from the treatment. Worse still, many immunotherapy patients experience moderate to severe adverse side effects. Furthermore, it is often the case that in the absence of up-to-date actionable information on the individual patient's cancer, a cocktail of drugs, with a long list of adverse side effects, are prescribed in the hope of improving cancer treatment response.

Using liquid biopsy to evaluate patient-specific information on an ongoing basis, including potentially actionable markers, will allow better patient selection by identifying which patients have the greatest chance of benefiting from targeted drugs. This will not only improve an individual patient's chance of response and potentially improve their quality of life through the reduction of unnecessary adverse side effects when a drug is no longer effective, but also dramatically reduce overall patient treatment costs.

This is critical for healthcare systems struggling with an ageing population and increasing healthcare costs, and on an individual basis for patients funding their own medical treatment. This approach will support the efforts of the National Institute for Health and Care Excellence (NICE) in the UK, and similar global organisations assessing the cost-effectiveness of medicines, to ensure effective use of financial resources.

Liquid Biopsy – A Rapidly Emerging Market

The liquid biopsy market is an area of rapid growth. Back in 2014, Cowen and Company estimated that the market opportunity could exceed $10bn annually by the end of the decade.[20] In their more recent market analysis (2020), it was estimated that the liquid biopsy market could be worth up to $130bn annually in the US alone. Cowen and Company identified five main areas for the promising application of liquid biopsies, including asymptomatic screening, high risk screening, therapeutic selection, recurrence monitoring and biopharma drug development.[7]

Conclusion

Liquid biopsies are less invasive, costly and time-consuming for patients compared to the current 'gold standard' of solid tissue biopsies. They can provide vast amounts of information to help address the ever-changing challenges of cancer heterogeneity by providing real-time insights into an individual patient's cancer status. The ability to identify mutations and actionable drug targets using a liquid biopsy sample enables more appropriate, and therefore more effective, personalised treatment, allowing for the reduction of adverse side effects and streamlining of drug costs.

Repeating liquid biopsies throughout the patient care pathway could have a profound impact in understanding cancer evolution, response to treatment and relapse status.

In the clinic, liquid biopsy has the potential to support the advancement of personalised patient care pathways whilst improving patient experience and reducing subsequent healthcare costs

Overall, liquid biopsies have the potential to provide, through a simple peripheral blood test, crucial medical information that can be harnessed to aid the treatment of cancer by affording a better view of tumour heterogeneity and facilitating personalised patient care pathways. The successful use of liquid biopsies in clinical practice will enable clinicians to better manage a patient's disease and enable a more rational use of targeted therapies, while offering patients peace of mind and an improved quality of life.

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