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Liquid biopsy for HER2-positive breast cancer brain metastasis: the role of the cerebrospinal fluid

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Cell-free tumour DNA (ctDNA) released from tumours has changed the paradigm for non-invasively identifying and monitoring genomic alterations of patients with cancer.[1 2] For patients with brain metastasis, however, plasma ctDNA may not reflect the central nervous system (CNS) tumour burden.[3] The cerebrospinal fluid (CSF), which is often directly or indirectly in contact with brain tumours, has been explored as a 'liquid biopsy' and as source of genetic material derived from brain tumours.[3–5]

In this edition, Siravegna *et al*[6] report the molecular results of liquid biopsies from a patient with epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer, who developed CNS progression and leptomeningeal carcinomatosis at a time when the systemic extracranial metastases showed clinical radiological response to treatment with ado-trastuzumab emtansine (T-DM1). T-DM1 is an antibody-drug conjugate that combines the antitumour properties of the trastuzumab (a humanised antihuman HER2 antibody) with the maytansinoid, DM1, a potent microtubule-disrupting agent, joined by a stable linker.

Paired ctDNA from the CSF (CSF ctDNA) and from plasma (plasma ctDNA) were genomically characterised before and after the fourth line of systemic therapy with T-DM1. The paired analysis of CSF ctDNA and plasma ctDNA mirrored CNS and systemic extracranial tumour burden, respectively. *ERBB2* amplification, a hallmark for HER2-positive breast cancer, *MYC* amplification and mutations in breast cancer driver genes (ie, *PIK3CA* and *TP53*) were enriched in the CSF ctDNA as compared with plasma ctDNA. That possibly reflects the magnitude of CNS infiltration or high tumour burden in the CNS identified as per CSF ctDNA.

The case study provides evidence of divergent CNS and extracranial responses that are identified by different sources of non-invasive tumour-derived ctDNA. The persistent high levels of ctDNA in the CSF at the T-DM1 post-treatment timepoint measurement revealed that the patient had CNS progressive disease. By contrast, decreasing mutant allelic frequencies of selected mutations in plasma ctDNA reflected partial clinical response in extracranial metastases. The discrepancies in CNS and extracranial responses represent a problem with modern targeted systemic therapies, particularly in the context of HER2-positive breast cancer. Some anti-HER2 therapies (eg, trastuzumab) tend to control systemic disease, but to spare the CNS as they do not penetrate the blood–brain barrier well, and are not retained in the CNS. Lapatinb combined with capecitabine[7 8] and T-DM1, on the other hand, have shown some in-brain tumour activity.[9]

Previous studies have explored the CSF ctDNA as a 'liquid biopsy' to more precisely characterise and monitor brain cancers, considering the lack or minimal levels of CNS-derived ctDNA present in the plasma.[5 10–12] Somatic alterations have been identified in the CSF ctDNA of patients with brain malignancies in 50%–75% of the cases.[5 10–12] In a series that included analyses of multiregional metastatic sites from post-mortem specimens of patients with breast cancers with brain metastasis and primary brain tumours, CSF ctDNA and plasma ctDNA were compared.[5] The genomic alterations of CNS disease were better captured by CSF ctDNA than by plasma ctDNA.[5] Notably, in the case of highly disseminated systemic metastatic disease, plasma ctDNA was shown to capture the repertoire of mutations from both CNS and extracranial metastases; by contrast, CSF ctDNA was a suitable tool for identifying genomic alterations of patients with absent or minimal extracranial tumour burden.

The authors of the present article suggested that ctDNA was more informative and sensitive

than radiologic imaging. However, detailed information on CNS or peripheral tumour volume measurements was missing. In addition, the authors were not able to comment on whether ctDNA anticipated a clinicoradiological response because CSF ctDNA was not collected systematically over a longer follow-up. Previously, the measurement of tumour volume was shown to correlate with plasma variant allele frequency.[13] As for patients with primary brain tumours and brain metastasis, CSF ctDNA was shown to be modulated over time, following the same trend as the variation in brain tumour burden and also complementing the diagnosis of leptomeningeal carcinomatosis.[5]

The case study also alludes to spatial tumour genetic heterogeneity, in which each histological component of the mixed primary breast tumour (micropapillary and invasive ductal NST (non-special type)) had a specific repertoire of mutations. The micropapillary component had a *PIK3CA* mutation that was detected in the CSF with high allelic frequencies. It was hypothesised that this aggressive component might have given rise to brain and other distant metastasis. However, only a thorough analysis using systematic brain tumour multisampling in post-mortem specimens would have provided firm evidence for spatial tumour heterogeneity in this case. Combined histological analysis and highly depth sequencing could then be performed in the brain and extracranial implants to permit confirmation of whether they had originated from the micropapillary or invasive ductal NST components of the primary breast cancer.

This is important because even though the genomics landscape of primary breast cancer has been well described, less is known about metastasis from breast cancers.[14–18] Brain metastasis from breast cancers may be clonally related to their primary tumour but may acquire driver mutations later on and harbour clinically actionable mutations that are not detected in primary tumour samples.[15 16] Therefore, the use of CSF ctDNA may be important as a real-time and organ-specific approach to identify the genomic alterations in the brain site in addition to plasma profiling.

In the context of HER2-positive breast cancer with brain and systemic extracranial metastasis, 'liquid biopsies' are not ready yet to substitute radiological imaging or to stratify patients for specific targeted therapies. However, the combined analyses of CSF, plasma and radiological imaging may benefit patients with HER2-positive metastatic breast cancer with discordant in-brain and extracranial responses, potentially outlining tumour genetic heterogeneity, clonal evolution and mechanisms of resistance to explain such clinical discordances. CSF ctDNA has the potential to identify brain metastasis-specific actionable genomic alterations that may facilitate the design of personalised treatments to target brain metastasis.

Competing interests None declared.

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