The promise of liquid biopsy in cancer: a clinical perspective

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Abstract: The clinical utility of liquid biopsy in cancer treatment will increase as circulating tumor cells (CTCs) analysis move from the enumeration to the real-time measurement of tumor characteristics. Intratumor heterogeneity is becoming increasingly recognized as a major drawback to the shift to personalized medicine. Spatial and temporal heterogeneity might be reflected by the serial assessment of CTCs. Indeed, the developing technologies for CTCs analysis now allow digital genomic and next-generation sequencing approaches, able to differentiate molecular subtypes of the disease and to monitor genetic variation over time. The liquid biopsy of cancer might offer a real-time assessment of tumor biology, providing the opportunity to serially evaluate patients most likely to benefit from targeted drugs based on a dynamic characterization of the disease at the molecular level. Although hurdles remain before liquid biopsy is seen in routine clinical practice, the information derived from CTCs may facilitate the real-time identification of actionable mutations in cancer leading the way toward personalized medicine.

Keywords: Circulating tumor cells (CTCs); breast liquid biopsy cancer

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Case report No.1

In a 52-years-old woman was found a pleural and abdominal metastatic breast cancer: a biopsy was performed and pathology showed ER and PR positive, Ki67 50% and HER2 positive cancer. This lady had, 3 years earlier a stage I breast cancer, ER and PR positive, Ki 67 20% and HER2 negative. She received adjuvant hormonal therapy. At the time of relapse a liquid biopsy was performed and circulating tumor cells (CTCs) showed to be triple negative.

Unfortunately at the time of surgery no liquid biopsy was performed.

Case report No.2

A patient with primary diagnosis of triple negative breast cancer (ER PgR, HER2-negative). A patient with primary diagnosis of TNBC came for the first time to our attention in February 2014. Cancer was already at stage IV (multiple hepatic and bone metastases). Notably, the first test conducted on the number of circulating tumor cells after about 21 days from the end of the first cycle of chemotherapy, showed an increase of the number of CTC. According to the data of the SWOG S0500 study, prognosis was bad. The patient died in December 2014. Although several lines of therapy have been administered, no clinical response was observed according to RECIST criteria. In particular, no therapy has proven to be able to lower the number of CTC. The last CellSearch analysis revealed more than 600 CTC/7.5 mL. Then the sample was sorted with DEPArray™ system, for single cell analysis. Twelve pure single CTCs were recovered, along with a pool of 10 CTCs and few WBCs, as control for genetic trough next generation sequencing. The PIK3CA COSM755 somatic mutation, was detected in homozygosity in 100% of CTCs.

The clinical management of cancer patients in advanced disease implies the knowledge of at least two different realities: the first is the best characterization of the patient and his cancer; the second is the most appropriate treatment and the evaluation of its activity and efficacy.

The characterization of the patient is determined by its medical and social history and from the extension of

neoplastic disease determined by clinical examination and radiological exams. The characterization of the tumor is made at the time of the initial diagnosis and at disease progression, whenever possible, if a metastasis would be accessible to a non-invasive biopsy. The choice of the most appropriate treatment is increasingly based on biological and molecular characterization. This approach poses at least a few basic problems: the spatial heterogeneity within the same tissue and/or sites of metastasis, and a prospective longitudinal heterogeneity in the context of biopsies performed in sequential time periods of the cancer natural history (1,2).

Sequence of different chemo and targeted therapies is part of a rationale which does not take into account, the molecular evolution of tumor mainly because of the difficulty of getting sequential biopsies at each time point of clinical reevaluations and therapeutic decisions. Studies on liquid biopsies have often demonstrated a different biomolecular characterisation compared to the tissue taken through "solid" biopsies leading to a possible dichotomy between the rationale of the ongoing therapy and a possible different rationale based on the CTCs characteristics (3). On the assumption that CTCs might drive the metastatic process, the optimal therapeutic strategy might be defined on the basis of longitudinally repeated liquid biopsies (4,5).

This clinical paradigm shift might allow to select the most appropriate treatment in parallel to the real time monitoring of the molecular evolution of cancer (6-8).

Back to the case report No.1: which biological and molecular pattern is supposed to be the real driver of the metastatic process in the first patient? Is it the HER 2 or the triple negative? In which pattern are we supposed to trust? At this time there is no doubt that the therapeutic choice will be based on the HER2 pattern, but it is very possible that in a near future we'll have enough experimental and clinical experience to be guided through the CTCs molecular pattern.

Back to the case report No.2: might the PI3KCA mutation found in all CTCs constitute the driver pathway of metastatic process (9)?

Patient's clinical management will still remain our main duty, but the feeling and perspection with the biology of their cancer disease will change: no longer what we see and what we can resect or biopsy, no longer or not only solid biopsies, but increasingly more the repeated liquid biopsies and their sequential analysis (10,11).

The main point is methodological again: which liquid biopsy, which molecular characterizations, and most importantly, which clinical trials are needed to confirm this change of clinical and diagnostic paradigm (12,13). The feeling is that a real liquid biopsy, to be useful for clinical purpose, should be able to guide decision making, instead of being a simple prognostic tool, and CTC enumeration which our molecular oncologists have for long time performed in our patients was actually designed as a prognostic test (14). We are now moving inside new technologies (15), some of which, in a surprisingly easy manner, are able to present CTC on a glass slide, ready to be used by pathologists using conventional staining, and in the meantime may allow DNA extraction for mutational analysis (16).

It is undoubtedly a revolutionary paradigmatic shift, but it is due by a long time: if we continue to talk about the personalization of cancer treatments, this so called "customization" cannot go through without a sequential liquid biopsy-based approach.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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