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EDITORIAL
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LIQUID BIOPSY IN ONCOLOGY: MYTH OR REALITY?

BIOPSIA LÍQUIDA EN ONCOLOGÍA: ¿MITO O REALIDAD?

Antonio Russo[1], Antonio Galvano[1]

EDITORIAL

One of the most relevant challenge in oncology would be the ability to deeply know tumoral genetic aspects through technological innovation and translational research to be finally able to personalize oncological treatment based not only on classical patient's clinical characteristics but also on its tumoral genetic portrait. In the last few years, many studies showed that to select cancer patients for a specific drug on the basis of specific genetic alterations could determine the greatest potential clinical benefit for a longer time, compared to treatment with the classic cytotoxic chemotherapy. Thus, oncology moves from the classic "one size fits all" approach, which provided classic chemotherapy agents on the basis of the cancer primary site and its histological type, to a new classification based on the tumor molecular profile. The characterization of the genetic alterations of the tumors, and the understanding of the complex interaction between the molecules of the same network represents, therefore, the rationale on which precision medicine is based. These advances have been made possible by the recent development of new technologies, such as next generation sequencing (NGS) or massive parallel sequencing (MPS), which allow the sequencing of larger gene portions compared to previous technologies, with reduced times and an increase in analytical sensitivity. The potential of these platforms in clinical practice is linked both to the analysis of cells on tumor tissue and to the analysis of circulating tumor DNA (ctDNA) contained in circulating free DNA (cell free DNA, cfDNA) which can be isolated from peripheral blood and biological fluids (liquid biopsy), instead of neoplastic tissue. However, in complex tumor biology, it is not enough to identify a genetic alteration to be sure that it can represent a predictive factor of response or therapeutic resistance: the presence of a genetic alteration and the availability of a drug directed against that alteration are only preconditions for effectiveness. There are, in fact, "driver" mutations and "passenger" mutations; and although many neoplasms depend on a single oncogene for their growth and survival (according to the theory of "oncogene addiction" or "oncogene driver"), the selective pressure exerted by medical treatment on the network of intracellular signals can determine the hyperactivation of compensating pathways and alternative pathways that result in a suboptimal modulation of the target pathway. Another critical point that can represent an obstacle to precision medicine is tumor heterogeneity: the tumor genome dynamically evolves over time and accumulates genetic alterations in different cell sub-clones. This translates into an intratumoral heterogeneity both spatially, i.e. between the primary tumor and the metastatic sites (or, even, within the tumor nodule itself), and in a temporal heterogeneity, or the bio-molecular characteristics of the neoplasm may vary in time. In this perspective, liquid biopsy could represent a useful tool for obtaining a dynamic picture of the molecular evolution of the disease. The main field of application of liquid biopsy to date is represented by the identification of predictive factors in patients with advanced disease and is currently used in clinical practice for the mutational analysis of the Epidermal Growth Factor Receptor (EGFR) and/or T790M gene in patients with Advanced non-small cell lung cancer (NSCLC). In particular, liquid biopsy can routinely replace standard tissue biopsy if tissue biopsy is technical impossible at diagnosis of advanced NSCLC or in patients progressing after a first (gefitinib or erlotinib) or second (afatinib) generation tyrosine-kinase inhibitors (TKI) in order to determine the T790M mutational status that is considered predictive for third generation TKI (osimertinib) efficacy. The effort of the scientific community is now to transfer the genomic and proteomic knowledge of basic research to clinical practice, to provide clinically relevant information for choosing a personalized treatment, with a view to precision medicine. In fact, although the liquid biopsy is able to more fully

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represent the molecular heterogeneity of the disease compared to the tissue biopsy, potentially containing tumor DNA deriving from the different areas of the same tumor, in the presence of tumor heterogeneity, it provides little information on the representativeness in the context of the tumor of the biomarker identified. Other potential limitations of liquid biopsy could be related to false negative (Insufficient DNA shed into plasma, insufficient sensitivity in older assays) or false positive (wide time interval between tissue and sample sampling, white blood cells contamination and tumor heterogeneity) conditions. Finally, the new diagnostic-therapeutic approach to neoplasms, which integrates clinical-pathological criteria with molecular analyzes, is also reflected in clinical trial designs: precision medicine has meant that clinical trials relating to new drugs with a molecular target, have become difficult to conduct through the classic designs of controlled clinical studies: the classification based on the molecular profile causes a segmentation of the neoplasms into numerous molecular subtypes, which include subgroups of few patients. Therefore, new designs of clinical trials have been developed, such as the "Basket" and "Umbrella trials", in which patients are recruited on the basis of the genetic and molecular characteristics of the neoplasm, with the aim of giving treatment only to patients potentially more responsive, reducing the use of ineffective and in any case toxic drugs, as well as the development time of new drugs and the associated costs. These trials resulted in two recent "agnostic" approval for larotrectinib and pembrolizumab for all patients who carried molecular alteration on NTRK fusion gene or who carried microsatellite instability respectively, irrespective of the primary tumor site. These represented the paradigm of a new era in oncology in which every patient will receive a tailored new generation therapy according to its own tumor genotype. Of course, as it is easy to imagine, these in-depth analyzes of the tumor genome will provide an always greater amount of genetic information for many of which an adequate cancer treatment is not yet available. It is for these reasons that the institutional tumor boards must recruit molecular biologists and pathologists which will therefore constitute the so-called molecular tumor boards whose usefulness will be essential for the correct interpretation of the bioinformatic data in order to determine the most appropriate therapeutic choice for every oncological patient.

EDITORIAL

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