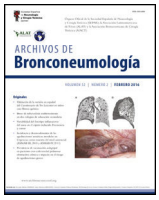
Arch Bronconeumol. 2019;55(6):289–290

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Lung Cancer and Liquid Biopsy: Realities and Challenges in Routine Clinical Practice☆

Cáncer de pulmón y biopsia líquida: realidades y retos en la práctica clínica

Laura Muinelo-Romay,[a,*] Jorge García-González,[b] Luis León-Mateos[b]

[a] *Unidad de Análisis de Biopsia Líquida, Oncología Médica Traslacional (Oncomet), CIBERONC, Instituto de investigación Sanitaria de Santiago de Compostela (IDIS), Santiago de Compostela, Spain*

[b] *Departamento de Oncología Médica, Complejo Hospitalario de Santiago de Compostela, SERGAS, Santiago de Compostela, Spain*

During recent years we have seen a real revolution in the clinical management of patients with lung cancer. One of the main reasons for the changes, apart from the emergence of immunotherapy treatments and new targeted therapies, is the significant progress made in liquid biopsy analytical techniques. Liquid biopsy refers to any biological fluid that contains tumor material that can be characterized at the molecular level. In this respect, it is important to note that although blood is the most widely used type of liquid biopsy, other fluids such as pleural fluid or saliva can provide valuable information for diagnosis, treatment selection, and monitoring of patients with lung cancer.[1]

The main value of liquid biopsy analysis lies in the fact that these samples are accesible and can be obtained at different points over the course of the disease. These samples give a comprehensive picture of the disease, since they contain material released by different tumor locations present in the patient. This is particularly important for the management of lung cancer patients, due to the difficulty in obtaining tissue samples, the need of a deep molecular characterization to select the adequate targeted therapy and the rapid development of resistance mechanisms, that characterizes these tumors.

There are currently four main circulating targets used as liquid biopsy in lung cancer: circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), circulating exosomes, and platelets.[1,3] Of these, the only one currently used in clinical practice is the ctDNA. Tumor cells release fragments of DNA into the bloodstream, mainly due to cell apoptosis and necrosis.[4] These fragments of tumor DNA usually constitute less than 0.1% of all circulating DNA, so highly sensitive techniques, such as digital PCR or new massive sequencing techniques, must be used to detect them. These techniques can detect point mutations, copy number viariation or small indels, with a sensitivity of nearly 0.01%–0.001%.[1,2] Therefore, nowadays just with a simple blood test EGFR mutations can be analyzed to select patients that will benefit from the treatment with tyrosine kinase inhibitors.[5] In fact, the ESMO guidelines recommend the use of liquid biopsy for the determination of the T790M resistance mutation in patients with non-small cell lung cancer for whom no tissue sample is available.[6]

In addition to the value of ctDNA analysis for guiding therapy selection, several studies have shown that it can be used to closely follow-up lung cancer evolution, monitoring the levels of specific somatic mutations in each patient.[2,7] This means that we can monitor clonal evolution, response to treatment, and the development of resistance months before progression is perceptible on imaging studies.[8] In patients with lung tumors resected with curative intent, we can also determine the presence of minimal residual disease.[9] Furthermore, the analysis of the mutational load using ctDNA techniques is one of the most promising tools to guide the selection of immunotherapy, independently or in combination with the expression of the checkpoint inhibitor, PD-L1.[10]

CTCs are the disadvantaged b̈rotheröf ctDNA. These cells can escape from the primary tumor or metastasis and reach the bloodstream. Most die from the action of the immune system and activation of anoikis processes, but some survive, extravasate, and reach and penetrate distant organs where they form a new tumor focus. Although these cells were first described in 1869, no sufficiently sensitive or specific techniques for their isolation were available until around 20 years ago. This was when the first studies using the CellSearch system (Menarini) appeared, and this system remains the only FDA-approved CTC quantitation test that can be used in metastatic colon, breast and prostate cancer.[1] In both small cell or non-small cell lung cancer, CTCs levels higher than 5/7.5 ml of blood are associated with worse rates of progression-free and overall survival in patients with both localized and metastasic tumors.[11] But even more valuable than the simple enumeration of CTCs is their molecular characterization. Various studies have characterized CTC populations in patients with lung cancer at the genome and transcriptome level, providing data of great interest for the development of new therapies.[12,13] It is also important to highlight the scientific milestone represented by the generation of murine tumor models derived from CTCs.[14] These models showed that

☆ Please cite this article as: Muinelo-Romay L, García-González J, León-Mateos L. Cáncer de pulmón y biopsia líquida: realidades y retos en la práctica clínica. Arch Bronconeumol. 2019;55:289–290.

* Corresponding author.
E-mail address: laura.muinelo.romay@sergas.es (L. Muinelo-Romay).

these cells were tumorigenic, and paved the way for the development of preclinical models that can be used for personalized drug screening without the need for a solid tumor sample. Unfortunately, the low efficiency of these models generation limites their application to research.

Another important source of tumor information is found in the exosomes, small vesicles, that contain DNA,RNA and proteins, which are released by the tumor cells in order, among other things, to foster tumor spread. Various studies have demonstrated the usefulness of analyzing circulating exosomes as a prognostic marker in lung cancer.[15] Platelets can also assimilate fragments of malignant genetic material, so they too represent an interesting approach in the characterization and monitoring of lung cancer.[15]

Fortunately for oncologists and their patients, the field of liquid biopsy in lung cancer is advancing rapidly, although further progress must be made in the development of standardized protocols and a better definition of the clinical benefit provided by the use of these techniques is necessary. It is clear, however, that these techniques will be key to offering more accurate and effective oncological medicine over the next years.

References

1. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. Nat Rev Clin Oncol. 2017;14:531–48.
2. Calabuig-Fariñas S, Jantus-Lewintre E, Herreros-Pomares A, Camps C. Circulating tumor cells versus circulating tumor DNA in lung cancer-which one will win? Transl Lung Cancer Res. 2016;5:466–82.
3. Köhn L, Johansson M, Grankvist K, Nilsson J. Liquid biopsies in lung cancer-time to implement research technologies in routine care? Ann Transl Med. 2017;5:278.
4. Stroun M, Lyautey J, Lederrey C, Olson-Sand A, Anker P. About the possible origin and mechanism of circulating DNA apoptosis and active DNA release. Clin Chim Acta. 2001;313:139–42.
5. Wu YL, Tong RZ, Zhang Y, Hu BB, Zheng K, Ding ZY, et al. Conventional real-time PCR-based detection of T790M using tumor tissue or blood in patients with EGFR TKI-resistant NSCLC. Onco Targets Ther. 2017;10:3307–12.
6. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29 Suppl. 4:iv192–237.
7. Marcq M, Vallée A, Bizieux A, Denis MG. Detection of EGFR mutations in the plasma of patients with lung adenocarcinoma for real-time monitoring of therapeutic response to tyrosine kinase inhibitors? J Thorac Oncol. 2014;9:e49–50.
8. Abbosh C, Birkbak NJ, Swanton C. Early stage NSCLC – challenges to implementing ctDNA-based screening and MRD detection. Nat Rev Clin Oncol. 2018;15:577–86.
9. Ludovini V, Pistola L, Gregorc V, Floriani I, Rulli E, Piattoni S. Plasma DNA, microsatellite alterations, and p53 tumor mutations are associated with disease-free survival in radically resected non-small cell lung cancer patients: a study of the perugia multidisciplinary team for thoracic oncology. J Thorac Oncol. 2008;3:365–73.
10. Gandara DR, Kowanetz M, Mok TSK, Rittmeyer A, Fehrenbacher L, Fabrizio D, et al. Blood-based biomarkers for cancer immunotherapy: tumor mutational burden in blood (bTMB) is associated with improved atezolizumab (atezo) efficacy. Ann Oncol. 2017;28 Suppl. 5. Abstr 1295O.
11. Mohan S, Chemi F, Brady G. Challenges and unanswered questions for the next decade of circulating tumour cell research in lung cancer. Transl Lung Cancer Res. 2017;6:454–72.
12. Park SM, Wong DJ, Ooi CC, Kurtz DM, Vermesh O, Aalipour A, et al. Molecular profiling of single circulating tumor cells from lung cancer patients. Proc Natl Acad Sci U S A. 2016;113:E8379–86.
13. Mariscal J, Alonso-Nocelo M, Muinelo-Romay L, Barbazan J, Vieito M, Abalo A, et al. Molecular profiling of circulating tumour cells identifies Notch1 as a principal regulator in advanced non-small cell lung cancer. Sci Rep. 2016;6:37820.
14. Hodgkinson CL, Morrow CJ, Li Y, Metcalf RL, Rothwell DG, Trapani F, et al. Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer. Nat Med. 2014;20:897–903.
15. Bracht JWP, Mayo-de-las-Casas C, Berenguer J, Karachaliou N, Rosell R. The present and future of liquid biopsies in non-small cell lung cancer: combining four biosources for diagnosis, prognosis, prediction, and disease monitoring. Curr Oncol Rep. 2018;20:70.