Journal of Lung Cancer Diagnosis & Treatment

de Macedo et al., J Lung Cancer Diagn Treat 2017, 2:3

Opinion

OMICS International

ct DNA - What is it´s Advantage in Clinical Practice in Lung Cancer at the Present Time

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Received date: July 31, 2017; **Accepted date**: September 04, 2017; **Published date**: September 11, 2017

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For long, tissue biopsy in solid tumours has been the gold standard for histological, immunochemistry, genetic and molecular diagnosis of cancer. Traditionally, anatomic and pathological and also imagological tools have permitted, in combination, a precise evaluation of solid tumours and it's classification by TNM staging. Consequently, treatment modalities may be tailored.

Nevertheless, tumours are a heterogeneous disease that harbours different clones upfront within the same tumour, being one of them the main driver of carcinogenesis at the beginning of cancer history. Cancer is in fact, a dynamic disease with multiple complex genomic changes (primary or acquired mutations, gene rearrangements), that occur since the beginning of its "birth" that suffers changes due to its microenvironment. Namely aggressions to which they are submitted by different types of treatments chemotherapy, immunotherapy or target therapy). Main activating pathways of carcinogenesis are known nowadays, as well as bypass pathways or "second routs" that are well identified, when tumours are treated and submitted to different treatments. They are tailored by the way we threaten them, and find alternative ways, as mentioned above, to achieve carcinogenesis aim: proliferation, angiogenesis, migration and survival.

The aim of this review is how translational research can help as overcome more efficiently, with less costs, and real time assessment of cancer, in a more refine approach to each of these challenges, aiming for precision medicine.

New Perspectives

Recently cancer diagnosis and follow-up in solid tumours has been revolutionized by a new concept of questioning what is happening in the blood of cancer patients, since diagnosis, monitorization during follow-up in surgical cases, in the metastatic context in monitoring progression, resistance to treatment and also, quantify minimal residual disease. This concept of liquid biopsies technology allows us to collect circulating cancer cells or DNA fragments from tumours that are shed into the bloodstream. We shall focus in circulating cell-free tumour DNA (ctDNA) as the most advanced clinical method used at the present time.

In lung cancer many trials are ongoing to approve determination of ctDNA as a prognostic and predictive factor either in early surgical stage or in metastatic stage. Some ongoing studies will be focused ahead. The main difficulty in lung cancer patients is the access to new tissue biopsies for they are operator dependent, difficult access in some cases, insufficient amount of tissue for analysis and painful procedure. In fact determination of ct DNA has many advantages [1].

The determination of ctDNA in human blood has for long been studied, and was first reported in 1948 [2]. The first challenge was to consider which digital techniques should be used, and next generation sequencing (NGS), has been accepted as the first option. Only last May 2017 were the guidelines for NGS validated by the College of American Pathologists, by the Association of Molecular Pathology as well as the European Society of Pathology [1]. Only recently has it been added to the testing approaches of NSCLC by the NCCN, although validated, it is yet not considered a standard of care. Even so, many studies have been already developed and are ongoing over the past 5 years, to re-inforce the impact of liquid biopsies as a whole, as a last minute reality to aim at 100% in precision medicine in the era of personalized medicine [3].

Surgical Stages and the Risk of Recurrence

Early-stage patients submitted to surgery with a curative intention are the most desirable patients for ct DNA analysis. Screening upfront either tumour burden in circulation, risk of metastatic relapse (prognostic value) and diagnosis of early relapse are the main objectives. Early ct DNA detection has for long been correlated to tumour recurrence and metastasis, as well as rising levels of ct DNA, allowing detection of progression and also tumour mutations in special

genes [4,5]. Identification of such mutations has a predictive value in selection of target therapies.

In these kind of patients where adjuvant chemotherapy is marginally beneficial or in those cases where adjuvant chemotherapy isn't recommended, the question is, if ct DNA is detected in these patients, should they be offered adjuvant treatment or not? Clinical trials must be performed to address this point. Or should patients be labeled as high risk and be monitored more closely for relapse? On the other hand, those patients with indication to perform adjuvant chemotherapy, for having adverse prognostic factors, what is the correct timing to obtain ct DNA during monitoring, besides clinical and imaging follow-up. Studies most be performed to address many questions also in the curative context of this disease.

Some pivot studies have been performed in stage I lung adenocarcinomas, where the impact of EGFR mutations on the prognosis of patients was evaluated. The authors concluded from a series of 583 patients submitted to curative surgery, that patients harbouring EGFR mutations, in completely resected stage I, had improved survival compared to wild-type patients. Patients in this cohort study with EGFR mutation had a positive prognostic factor, as the natural history of EGFR mutant tumours was better [6]. Other authors, evaluated the detection of EGFR mutations in pulmonary vein and peripheral blood plasma cell-free DNA for analysis of surgical treatment in early stage NSCLC. Eighty-nine patients were enrolled and pre-surgery peripheral blood samples and intraoperative pulmonary vein samples were collected. The study demonstrated that accurate detection of EGFR mutation from pre-surgical peripheral blood and intraoperative pulmonary vein in early stage cancer was demonstrated. The authors suggested that future monitoring the EGFR mutation abundance after surgery identifies patients, at risk for recurrence and could in future influence treatment options [7].

In the setting of curative patients many questions are left unanswered: Does circulating free tumour DNA in fact leave a trail in cancer patients submitted to a surgical curable procedure? Or, is there in fact a new classification of surgically resected lung tumor with positive or negative circulating free DNA? In other words, do patients harbor "oncological" DNA versus "healthy" DNA post-surgery? Many more studies must be performed to address many questions also in the curative context of the disease.

Metatstaic Disease and Identification of Resistance to Treatment

In the metastatic concept of cancer disease, patients submitted to different types of treatment in the era of personalized medicine, have been more than ever closely monitored by clinical, imaging and invasive procedures, in the scenario of early detection of progression due to treatment resistance. Determination of ct DNA by NGS has been performed in pilot studies with good results. Ct DNA analysis can reveal important information in the detection of tumour resistance to target therapies, changing the efficiency of target therapies, such as primary resistance or acquired resistance in mutations of EGFR gene in lung cancer [8,9].

The first study that approved detection of ct DNA test, for EGFR mutations in NSCLC favouring its clinical implementation, was based in a phase IV study (NCT01203917). One of the most important conclusions was that ct DNA could be considered for mutational analysis if tumour tissue was unavailable [10]. Other studies took place such as Rociletinib (CO-1686), an inhibitor of EGFR T790M, incorporated both tissue biopsies and liquid biopsies testing, to asses EGFR mutations, in patients were tumour sample was not available in some cases [11]. Some national studies performed, randomised 56 patients and evaluated the concordance between genetic alterations of tumour tissue DNA and ctDNA, the relation between variation of ct DNA and disease evolution, using NGS technology [12]. This study proved that NGS technology is feasible and that there is a good correlation between ct DNA and tumour DNA changes. The authors concluded ct DNA is useful for close monitoring and early detection of progression and detection of resistance to target therapy, supporting treatment decisions [13].

The main conclusion in the metastatic context is that ct DNA is becoming useful with direct impact in clinical and treatment decisions. Nevertheless, further studies are still needed to further validate this new diagnostic instrument into a routine basis application [14].

Future Perspectives

The challenging switch from turning ct DNA into a daily basis technique has been through a lightning change during the last few years. Extensive advances have been reached in so little time that science has given a gigantic step in favour of translational research. Recently, a European IMI consortium with more than 35 institutions called CANCER-ID, is now working in validating all liquid biopsy assays taking place [15].

Promising results have been obtained, but further studies with a bigger number of patients included is one of the main criticisms. Nevertheless, with ctDNA we get a wide view of the disease as a whole, evaluating its heterogeneity throughout time. On the other hand, a single tissue biopsy were only one snap-shot of the disease is taken, may mislead treatment decisions, because only a small clone may have been evaluated, missing or not the driver clone of the disease.

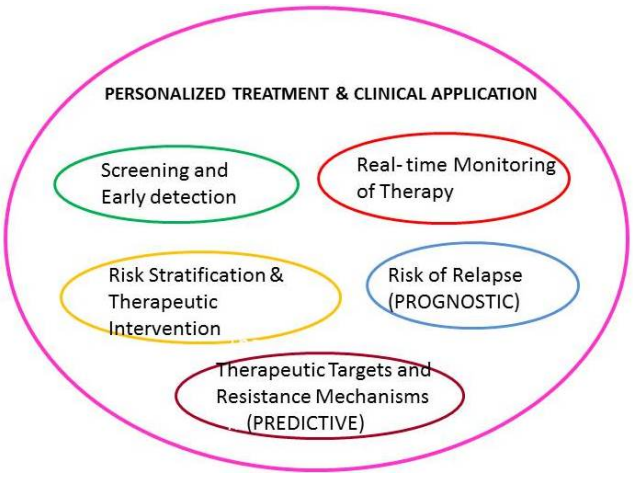

Figure 1: Clinical application of ctDNA in Personalized Medicine.

Many questions are still unanswered. Such as, which is the best timing to obtain ctDNA for screening ctDNA derived from resistant tumour clones? More studies are needed, to validate the clinical importance of liquid biopsies analysis in randomized clinical studies, where primary endpoints such as time to progression and overall survival are considered. A single snap-shot of circulating genome, is much more promising and representative of all the sub-clones of a

heterogeneous and dynamic disease, with genetic intelligence such as Cancer. Constant progress in the evolution of such technology and its prolific application in cancer care can only hold wide horizons for clinicians to improve personalized medicine, and above all, quality of care (Figure 1).

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