Commentary: Lukas Heukamp

Liquid biopsies transform lung cancer therapy

Understanding how genetic alterations drive tumour growth and progression in virtually all cancer indications is revolutionising cancer treatment. Modern medicine takes advantage of the weak points of a tumour by developing so-called targeted drugs. In lung cancer, more than a dozen genetic alterations with direct therapeutic implications are currently known. Compared with chemotherapy, targeted drugs open up more promising treatment possibilities. However they are only effective with respect to specific mutations. Therefore treatment selection needs to be based on these molecular characteristics. Fast and comprehensive molecular diagnostics are pivotal in making the most beneficial treatment decisions.

Traditionally, molecular diagnostics for targetable genetic alterations has been performed before treatment begins on tumour material obtained by biopsy. Every biopsy carries risks. The procedure is painful, costly and importantly, takes time. Analysis is routinely carried out in a sequential manner, with separate tests being performed on tumour slices. A mix of different technologies is needed to detect targetable alterations, from minor genomic changes such as point mutations, to large genomic rearrangements such as gene fusions or gene amplifications.

However, the increase in relevant genetic alterations has rendered sequential testing incompatible with today's clinical requirements. It is simply too time and material consuming, with often disastrous results for the patient. A recent survey of German oncologists revealed that more than 70% of all patients are tested for the most common and the most easily detectable alteration in lung cancer, the so called EGFR-mutation. However, due to the long turnaround times, in 35% of all cases treatment is initiated without taking the result into consideration. Furthermore, in more than 30% of all lung cancer patients, sequential testing cannot be completed due to insufficient material. Therefore, many patients receive possibly suboptimal therapy as test results are not available on time. Furthermore, for every third patient the opportunity for an effective targeted therapy may be missed entirely unless the patient agrees to undertake a risky re-biopsy to gather more tumour material.

The already limited supply of tumour tissue for diagnostics will become even more critical in the future, as more and more targeted drugs become available that will require additional genetic testing. Technologies such as '*hybrid capture based next generation sequencing*' are thus on the cusp of replacing sequential testing to meet today's clinical standards. This method can be performed on minimal amounts of tumour material, detecting all therapeutically relevant alterations in one go, rendering sequential testing obsolete. For analysis, all genes of interest are extracted from the total tumour genome using complementary probes. All targeted fragments are then sequenced simultaneously with high depth. This procedure also ensures high sensitivity for alterations occurring with low frequency against a high non-tumourous genomic background. Subsequent bioinformatics evaluation of the sequencing data can then be analysed for its therapeutic relevance.

The initial tissue analysis however is merely the first step in a molecular diagnostics protocol for optimal patient care. Cancer is known to evolve over time, and the ability of malignancies to develop resistance to drug treatment remains a substantial challenge in the clinical management of advanced disease. With targeted drugs available to overcome this resistance, the need for repeated molecular diagnostics over the course of treatment increases. New tools to monitor disease and to adapt treatment protocols are desperately needed. However, due to the health risks, repeated tissue biopsies are not feasible.

This puts the focus on blood-based genomic diagnostics, which has the potential to revolutionise cancer treatment. The idea is to obtain a complete picture of a patient's cancer from a simple blood sample, a so-called liquid biopsy. This offers what tissue analysis cannot do: the opportunity to take serial samples in order to monitor tumour genomic changes in real time. The physician is able to control the relevance of the treatment, and observe the emergence of resistance, sparing the patient the unnecessary toxicity of a drug that has ceased to provide benefit.

A liquid biopsy will also identify possible genomic differences between primary tumours and corresponding metastases, thereby capturing the entire heterogeneity of the disease and providing the physician with all the information he needs to adapt treatment accordingly.

Circulating tumour DNA (ctDNA) has been proven to be a feasible biomarker. These small fragments of DNA are shed into the bloodstream by the tumour and are found at relatively high concentrations in the blood of most patients with metastatic cancer and at lower but detectable concentrations in a substantial fraction of patients with localised cancers. This is in stark contrast to circulating tumour cells (CTC), which can be detected only in a fraction of patients with detectable ctDNA. Similar to tissue diagnostics, liquid biopsy analysis originally focused on detecting selected genetic alterations, for example, picking up only one possible resistance mechanism. As with tissue analysis, time to result is critical as the physician needs to be able to initiate the right treatment without delay. Therefore, just as in tissue diagnostics, comprehensive *hybrid capture* based next generation sequencing technologies are bound to be implemented and become the gold standard for liquid biopsy diagnostics. As far as we are aware, our company NEO New Oncology AG, is the only enterprise in Europe to offer hybrid capture liquid biopsy diagnostics. This gives the treating physician a medical report for making informed decisions involving treatments with targeted drugs.

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