Advances in Cancer Therapy: Liquid Biopsy

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Our growing understanding of the molecular and cellular mechanisms by which tumor development and progression occur has led to a paradigmatic change in cancer therapy. More and more targeted treatment options have been introduced into clinical practice. Some of these rely on the molecular evaluation of tissue biopsies, including sequencing analyses to identify appropriate target mutations. Examples are BRAF mutations in melanoma, KIT mutations in gastrointestinal tumors, or EGFR mutations in non-small cell lung cancer to use the respective inhibitors.

However, there are substantial drawbacks, making these approaches less effective as they were supposed to be. One major hurdle is the heterogeneity of tumor tissue. The position of the biopsy might not have picked up the most important progression driving mutation. Consequently, the therapeutic approach will not be successful. Also, over time the tumor might acquire additional mutations, either in the same target, which could lead to resistance, or in other targets, which might require different targeted treatments. Clonal diversity of the malignancy and changes of its molecular signature over time are important challenges and require a deeper insight into the biology of the tumor. Currently used diagnostic methods are not suited to match the needs. Furthermore, methods for early diagnosis of a possible relapse of the tumor will be a prerequisite for clinical decision-making.

Although substantial efforts are being made to increase the frequency of biopsies and to extend the number of loci, this will not be sufficient to gather all information needed for a rational and successful treatment. In addition, early detection of a developing tumor also requires novel strategies.

Over the last years, *liquid biopsies*, mainly drawn from the blood of cancer patients, have been investigated, as they promise to meet most of the requirements listed above. At present we are still in a very early phase of methodological development. Moreover, validation of the use of liquid biopsies in clinical practice is still in its very beginning.

Nevertheless, liquid biopsies have the potential to cause a paradigmatic change in cancer diagnostics and thus might be a key to better treatment of this life threatening disease. Tumors change

continuously over time, from the very first mutation that occurred within a single cell, by acquiring additional mutations. As a result, their developmental and metastasizing properties are subject to a dynamic process that eventually leads to the death of the patient. Therefore a dynamic monitoring of these changes is absolutely required to make the appropriate decisions for optimal treatment.

Tissue biopsies, taken from the primary tumor, reflect the molecular signature at the site from which and the time when the sample was taken. Thus, tissue biopsies are only snapshots from a defined spot. It cannot be excluded that important properties, e.g. the presence of very aggressive subclones, may remain undetected. Therefore dynamic methods that pick up this heterogeneity at any time are urgently needed. Furthermore, in many cases the acquisition of tissue biopsies is not possible. Also in these cases we need dynamic information of the status and the changes within these lesions over time.

Liquid biopsies contain quite a number of biomarkers derived from the malignant lesions and reflect to some degree the molecular properties of the disease. Circulating tumor cells (CTCs) are released from the tumor and intravasate into the bloodstream. Apoptotic and necrotic tumor cells release cell-free nucleic acid fragments into the circulation. Circulating tumor DNA (ctDNA), circulating micro RNA (cmRNA) fragments, usually approximately 19–22 nucleotides in length, and circulating mRNA have been identified as tumor biomarkers in the blood. In addition, exosomal miRNA was shown to contain information about the status of a tumor. As the amounts of CTCs as well as circulating nucleic acids are very low and in nucleic acids degradation is a relevant process, it is necessary to develop fast and reliable purification methods. Furthermore, the collection of genetic information from the circulating targets is a major task and numerous approaches are being implemented to optimize sequencing technologies. The most important aspect, however, is the validation of biomarkers obtained from liquid biopsies. Here, clinical studies with special emphasis on liquid biopsies are needed. So far, a first positive result has been reported: In 2016, the detection of *EGFR* gene mutations in ctDNA by the Cobas *EGFR* Mutation Test v2 achieved FDA approval as a prerequisite for treatment with erlotinib [1].

In the series of mini-reviews presented in this issue of ONCOLOGY RESEARCH AND TREATMENT, we have gathered a number of short overviews covering different aspects of this novel diagnostic approach with special emphasis on its clinical relevance. Mader and Pantel [2] cover the current status and the future perspectives of liquid biopsies in cancer. Höppner and Kulemann [3] report on the concept of CTCs to be used in neo-adjuvant and adjuvant therapy of esophageal cancer. Buder-Bakhaya, Machiraju, and Hassel [4] describe the status of using ctDNA as a means to improve treatment of metastatic melanoma.

Schwarzenbach [5] has summarized the informational impact of small non-coding miRNAs as diagnostic markers in breast cancer, and von Bubnoff [6] contributed a perspective view on the use of ctDNA in response prediction and as potential early biomarkers of relapse.

Disclosure Statement

The author declares no conflict of interests.

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