Editorial

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Circulating tumor DNA measurement: a new pillar of medical oncology?

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An essential feature of the current state-of-the-art cancer management is that it is multidisciplinary. Cancer is a disorder too complex to be cured with a single approach or by a single medical specialty. Practically all medical specialties are involved to a greater or lesser degree in the care of cancer patients, including laboratory medicine. However, for a long time laboratory specialties were represented mostly by pathology and the role of laboratory medicine itself was marginal [1].

The medical management of cancer patient consisting of administration of pharmaceutical agents or, on the contrary, withholding anticancer drugs until a later moment (or indefinitely), can be compared to a complex building structure supported by several pillars. These pillars consist of essential information sources that guide the treatment decision. Such pillars on which the practice of medical oncology relies currently include the clinical assessment of the patient condition, tumor histology, imaging studies or surgical assessment during the operative procedure. Despite all this information, there remains in many cases uncertainty about the future course of the disease and the need for therapy, and treatment decisions are often being made based on prior experience in other patients rather than the knowledge of the particular individual case.

Two papers in the current issue of *Clinical Chemistry and Laboratory Medicine* present comprehensive reviews on various aspects of the measurement of circulating tumor DNA (ctDNA) in patients with solid tumors. The topic of ctDNA is comprehensively reviewed by Hu et al. [2]. Important concepts are introduced such as minimal residual disease (MRD). MRD describes single tumor cells or micrometastases that cannot be detected by conventional imaging used in clinical practice in patients after complete removal of the primary tumor. Historically, the presence of MRD has been inferred based on clinical observations of metachronous distant metastases after an apparently curative surgery. In such cases it had to be concluded that microscopic residual disease must have been present at the time of surgery in the form of dormant cancer cells or micrometastases that have progressed to overt metastases over time [3, 4]. The term MRD, originally introduced in hematologic oncology, has in patients with solid tumors been for a long time a rather theoretical concept that was difficult to be addressed in a quantitative manner despite decades of research. The potential to measure and quantitate MRD is a potential breakthrough in the management of patients with early cancer. The ctDNA may also be used for analyses like next generation sequencing (NGS) that provide essential information guiding the patient management in early as well as in advanced disease settings. Hu et al. document a steep increase of papers on the topic of ctDNA. Clinical use almost always lags behind research publication, but this technology has currently reached the stage where it could fundamentally alter the patient management.

The ctDNA represents only a small proportion of the total free DNA in the circulation, and the distinction of ctDNA is a complex issue. The detection based on the presence of tumor-specific mutations is complicated by the huge number of such mutation in a given patient population. Another approach consisting of using DNA methylation analysis is reviewed by Wang et al. [5]. The advantages and disadvantages of the methods currently used are reviewed. Changes in DNA methylation patterns occur early in cancer development, and using methylation analysis for the detection of ctDNA may be of particular interest in cancer screening. Differences in methylation are also associated with molecular subtypes, but DNA mutation analysis may be of advantage in this context as it provides invaluable information regarding the presence of potential treatment target mutations. Methylation analysis may be also of advantage to detect MRD or provide prognostic information that may be helpful in determining therapeutic strategy in patients with early cancer.

From a point of view of medical oncologist, some aspects of ctDNA deserve to be highlighted. The measurement of

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ctDNA represents a new dimension in the clinical assessment of neoplastic growth that is, particularly in patients with early cancer, of equal, if not greater, importance than the radiological imaging which has been the cornerstone in the evaluation of the disease extent and dynamics during the time course. In fact, the determination of ctDNA is of fundamental importance in setting the strategy of systemic therapy in patients with early stage cancer by addressing the issue of MRD. Postoperative (adjuvant) systemic therapy has resulted in major improvements of outcome across a range of solid tumors. Similar to the treatment of patients with overt metastases, adjuvant systemic therapy is the treatment of disseminated (systemic) disease that, in contrast to patients with overt metastases, is not detectable by conventional imaging methods, and the presence of disseminated disease (MRD) in the form of single dormant cells or micrometastases is only supposed, based on prior clinical experience in similar cases. The decision on the administration of systemic adjuvant therapy is based on the likelihood of distant recurrence and prior clinical trials demonstrating improved outcomes in individuals with a given risk of recurrence. In each patient, the potential benefits must be carefully weighed against the risks associated with the treatment. This approach inevitably results in overtreatment of patients in whom the tumor was cured by surgery and who either have no microscopic disease or in whom microscopic disease would not manifest during the expected lifespan as well as in undertreatment of patients who harbor dormant tumor cells or micrometastases that would progress to clinically manifest metastases despite the tumor being classified as low-risk. The consequences of both the undertreatment and the overtreatment may be equally disastrous resulting in disease recurrence, or serious, even lethal toxicity, in subjects who have already been cured by surgery. The utilization of ctDNA determination in this situation may be exemplified by a recent trial in which patients with stage II colon cancer after curative surgery were randomly assigned to a decision on adjuvant chemotherapy based either on the standard clinical and pathological criteria or on the presence of circulating tumor DNA [6]. The use of adjuvant chemotherapy was almost halved in the arm in which decision was based on circulating tumor DNA analysis, but the recurrence-free survival was practically identical in both arms, providing proof of the concept for circulating tumor DNA guided decision in early colon cancer.

Serial determination of ctDNA could also be used for monitoring of patients after an apparently successful therapy. Currently, repeated radiological studies are used with the associated risks of stochastic effects, and in the population the use of imaging has to be carefully weighed considering these risks. Although the determination of circulating tumor markers is often used in this situation, it is not reliable in all cases, and ctDNA may prove to be superior for the detection of recurrence, but more studies are needed.

With the advent of targeted therapy, the determination of specific tumor mutations may be crucial in determining the therapeutic strategy. Histological examination of tumor tissue is still a requirement for the diagnosis of cancer before starting treatment in the overwhelming majority of cases, and molecular profile is usually determined using the biopsy specimen obtained for histological diagnosis. However, the size of the biopsy specimen could represent an important limitation in many instances. A classical example is non-small cell lung cancer (NSCLC). It is now evident that NSCLC is not a single disease entity, but rather a group of neoplasms originating from the same organ, but differing in the molecular pathogenesis and biological behavior. These differences are in many instances associated with the presence of targetable tumor gene mutations. Agents targeting these mutations, for example epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitors have transformed the natural history of tumors harboring these mutations from a rapidly fatal to chronic disease with median survival of several years. However, as the drugs targeting EGFR or ALK are active only in patients with the respective gene mutation, tumor mutation status has to be determined for each individual patient. In NSCLC biopsy is typically obtained during bronchoscopy, and the quantity and the quality of the specimen may not be sufficient for all molecular analyses that may be necessary [7]. The isolation and analysis of the ctDNA may compensate for the insufficient biopsy sample [8].

There remain still many fundamental problems and questions to be adressed. The sensitivity of each method is a major issue determining the use in clinical practice. The analysis of ctDNA may not be as important in patients with advanced cancer that is evident on imaging, but is of fundamental importance in patients with no evidence of disease in whom it may alter the treatment strategy as outlined above. The issues of threshold values along with specificity and sensitivity has to be addressed based on clinical experience in prospective trials.

As mentioned above, the management of cancer is a multidisciplinary effort with the strategy set for each case by a team that meets regularly at every institution that provides comprehensive cancer care. These multidisciplinary boards are usually shaped according the organ systems based on surgical specialties as the surgery still represents the cornerstone of treatment in most cases of patients treated with curative intent. With the advances in the understanding of the molecular pathogenesis and the advent of effective molecular

targeted agents the concept of tumor-agnostic oncology has emerged. Tumor-agnostic therapy means that tumors are not treated according to the primary site affected, but based on molecular characteristics. Usually only a small proportion of patients affected by cancer of each primary site harbor a specific molecular characteristic, but the same molecular change may also occur in tumors of other primary sites, and the patients with tumors bearing this molecular pattern are successfully treated across the range of primary sites. With the advent of tumor-agnostic cancer medicine molecular tumor boards have emerged in which specialists in laboratory medicine partner with medical, radiation and surgical oncologists, radiologists, pathologists and other relevant specialists and provide an important input for the decisions on the management of individual patients.

The technological advances of ctDNA determination and other methods, including NGS, open a plentitude of new opportunities in the management of cancer patients [8]. The applications in early diagnosis have been widely discussed and the potential benefit is obvious, but there are many other clinical scenarios where this new technology could provide essential clues. Take for example a patient with a history of cancer presenting with one or few lung nodules not accessible for transparietal or bronchoscopical biopsy. Currently the patient is offered either a surgical biopsy, an invasive procedure with associated risks, or observation with uncertain outcome. Future studies should determine whether ctDNA measurement could provide useful information in this setting. There are certainly many more other clinical scenarios in which ctDNA determination may prove being useful and that need to be explored.

In conclusion, the determination of ctDNA is transforming the practice of medical oncology. With the advent of these new technologies, laboratory medicine specialists have become an integral part of the multidisciplinary teams. Along with medical and surgical assessment, histology or imaging the analysis of laboratory data like ctDNA emerges as a new information pillar in medical oncology.

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