ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Importance of Circulating Tumor Cells in Diagnosis, Prognosis, and Treatment Selection

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H&O What are circulating tumor cells?

MA/GP Circulating tumor cells (CTCs) are cells that have broken off from the primary tumor or its metastases and are circulating in the bloodstream. Analyses of CTCs can provide a view of the tumor at every stage of the patient's disease, which was never before possible. CTCs are examined on 2 different dimensions: the number of CTCs and the molecular makeup of the cells.

H&O What role do CTCs play in oncology?

MA/GP CTCs have various diagnostic and therapeutic implications throughout the patient's disease process. CTC collection and characterization can be performed and yield useful information at diagnosis, during treatment, and post-treatment. One of the uses of CTCs is to stratify patients already in a clinical trial. For example, the presence or absence of CTCs could classify responders from nonresponders. CTCs can also be used as a stratification tool for inclusion or exclusion in the clinical trial itself. The molecular nature of the cancer as determined by CTCs could allow a selection of patients for a trial who are more likely to respond to a given therapy, thus excluding others from the trial. Accordingly, collection of CTCs may result in both lower costs and faster patient recruitment. Another way CTCs can be used is for diagnosis. In addition to staging a cancer based on its size and location, CTCs can provide information by predicting the true extent of the cancer's spread. CTCs can also be used to define response or resistance during therapy. In the metastatic patient, in whom the tumor may still be present, CTCs provide information about tumor burden, in particular concerning response or resistance to therapy. The final use for CTCs is in determining the recurrence or growth of the tumor after therapy by their presence and characterization.

The collection of CTCs allows the oncologist to determine the tumor burden at the initial diagnosis (helps in treatment decision making), at certain points after the therapy has begun (to see if the treatment is working), and post-therapy (to see if the cancer is recurring).

H&O What does the presence of CTCs suggest at different stages?

MA/GP The detection and enumeration of CTCs can be utilized as a prognostic marker in several tumor types, and it has been shown that a decrease in the number of CTCs correlates with response to chemotherapy. Conversely, an increase in the number of CTCs is associated with a lack of response and disease progression. This increase or decrease in the number of CTCs in the bloodstream provides some idea of what is occurring in the entire system. There is also evidence that the presence of CTCs, versus the absence of CTCs, at initial diagnosis suggests a poorer prognosis.

H&O What are the benefits of using CTCs as a prognostic tool?

MA/GP There are multiple ways oncologists can assess tumor burden, including physical exams, x-rays, computed tomography (CT) scans, magnetic resonance imaging, and various blood tests. CTC collection is a relatively easy and very sensitive way of assessing tumor burden. CTCs are collected by a simple blood draw and may be cost-effective compared to imaging modalities. CTCs also

allow us to use drugs more effectively because we can use the therapies in a more targeted manner.

The goal is to make CTC collection in cancer patients analogous to viral load and virus genotyping testing for AIDS patients. At each appointment, AIDS patients undergo a viral load test and genotyping to measure the amount of active HIV in the blood. These tests also indicate whether the medication is effective. We want to do the same thing with cancer: at every stage of the cancer process (diagnosis, during therapy, post-therapy), we want to assess the tumor burden by collecting CTCs in order to measure response to therapy or possible recurrence. After CTC collection, oncologists may want to use some other technology to confirm their findings or to gather more information. CTC analysis is a promising area of research because CTCs provide us with continuous, cost-effective, and minimally invasive access to the tumor that other tests do not provide.

There are a number of tools that oncologists currently use, most often in combination. For example, if there is evidence of tumor growth on a CT scan, an oncologist may then investigate that finding with a physical exam or a blood test. Over time, CTCs will take a much more prominent role in patient evaluation. However, I do not believe that physicians, in the near future, are going to abandon other types of testing. There is a need for more data that show the correlation between CTC testing and the tests that are currently used. Once this correlation is made, then we may see imaging and other tests being used with less frequency.

H&O Can you discuss the data on the gradient dual capture microfluidic chip diagnostic?

MA/GP There are 2 ways of capturing CTCs. One way is to take advantage of their size—they tend to be bigger than the other cells circulating in the bloodstream—and to create a method to trap the bigger cells while allowing the smaller cells to filter through. The other way to capture CTCs is to take advantage of the fact that CTCs have chemicals (antigens) on their surface that are unique to CTCs and not found in the blood elements. With this method, an antibody binds to the antigen and captures CTCs.

The chip we developed at On-Q-ity has a dual capture methodology, which uses both of these techniques. There are thousands of posts on our microscope slide–sized chip that get narrower as the blood flows down the chip. During this process, the normal blood elements, which are smaller, flow off the chip, and the CTCs, which are bigger, get stuck as the posts become narrower. The posts on the surface of the chip are also lined with an antibody against epithelial cell adhesion molecule (EpCAM), which is an antigen not found in blood elements but found on many CTCs. Some CTCs have more EpCAM on their surface than others, and the antibody captures those cells; the cells that have less EpCAM tend to be captured by the size method.

The dual capture chip can be coated with any antibody, as it is possible that there will be an antibody or a combination of antibodies that are more effective than EpCAM at capturing CTCs in certain types of cancers. For example, there may be an antibody that works better in prostate cancer and one that works better in colon cancer, so we could eventually have a chip that is tumor specific. It is a fairly straightforward procedure to run blood through the chip, and it is also a gentle process, allowing for further molecular characterization of the cells themselves. We have recently reported the data on the characterization of HER2 levels of breast cancer CTCs captured by our dual capture microfluidic chip. Our findings showed that the combination of antibody affinity and size filtration captured 65% of CTCs in blood spiked with human breast cancer cells compared to 45% captured by size alone and 16% captured by affinity alone.

H&O What is the future of CTC collection/detection?

MA/GP We know that the problem with the currently available technology is that in approximately half of patients, even in those with advanced disease, there are no CTCs that can be found. Thus, the idea is to capture the right number of cells in as many patients as possible. We are now analyzing different ways to make sure we capture a representative number of CTCs in each patient, and then characterize those cells. The opportunity we have with CTCs is to reshape the way cancer is being monitored so that it is done on a regular basis, allowing us to use our arsenal of therapies more effectively.

Suggested Readings

Merdek KD, Maimonis PJ, Dietenhofer K, Yen L, Palmer GA. A microfluidic device for the capture and HER2 characterization of circulating tumor cells from metastatic breast cancer patients. Paper presented at: 2010 Molecular Markers in Cancer Meeting; October 18-20, 2010; Hollywood, Florida.

Maimonis PJ, Merdek K, Dietenhofer K, Yen L, Palmer G. Affinity and size capture of circulating tumor cells: a platform for increased sensitivity. Paper presented at: 2010 AACR Molecular Markers Meeting; September 28-30, 2010; Denver, Colorado.