‘Liquid-Tumor Biopsies’ and the Future of Solid Tumor Oncology

A strong argument can be advanced that one of the critical distinguishing features associated with advances in the management of hematologic malignancies, in contrast to solid tumors, has been the ease of availability of ‘tissue’ during the *natural history of the illness* in the former to both study the biology of the malignancy and increasingly carefully monitor changes during the course of the cancer at the molecular level in individual patients.

It is currently ‘standard-of-care’, for example, to examine the blood or bone marrow to document the depth of a molecularly defined ‘complete response’ in patients with chronic myelocytic leukemia to both determine the extent of response and to document the presence of resistance to the current therapy long before there is any other evidence this event has occurred. Such early warning may permit critically relevant modifications in therapy that will favorably impact patient outcomes.

Further, in the not-so-distant past, there was almost always a substantial amount of cancer available from solid tumors to at least examine for the presence of unique genomic profiles at diagnosis. However, with the increasing use of minimally invasive procedures to confirm the presence of cancer and the subsequent relatively early delivery of systemic antineoplastic drug therapy in the natural history of a given malignancy, there may be limited (or

no) additional tissue present for laboratory-based investigation.

As a result, there has been considerable and increasing effort by academic and commercial groups to develop a reliable and clinically useful ‘liquid tumor’ biopsy strategy in a number of clinical settings. Such approaches have included both the examination of single cells (‘circulating tumor cells’) as well as free DNA in the blood that is suggested to originate from cancer present within the body.

The goals of these efforts are severalfold. First, simply the presence or a calculated number of ‘circulating’ cells might provide *prognostic data* regarding the individual cancer. Further, with evidence of progression, an alternative therapeutic strategy may be considered even before there is ‘clinical evidence’ (e.g., new or worsening symptoms, changes in imaging studies or blood-based biomarkers) of the ineffectiveness of the current management.

Second, and ultimately a far more relevant aim, it has been hoped that the particular molecular findings discovered within the blood from the circulating cells or DNA may permit a ‘window’ into unique molecular changes present within the individual patient’s cancer that will allow for the selection of specific ‘targeted therapeutics’ designed to favorably impact those abnormalities.

It is relevant to note the limited utility of pure *prognostic biomarkers* where there is no evidence such knowledge can be employed to alter the course of the illness. With the reasonable exception of the issue of the earlier discontinuation of an ineffective and possibly toxic antineoplastic strategy, how much does it really matter that one knows 'several weeks/months' earlier that the cancer has progressed when there is objectively nothing that can be done to alter the clinical course?

In contrast, if the information is shown to be *predictive* that a specific strategy may be of value in influencing the clinical course of a particular individual and in a manner not possible with conventional imaging or protein biomarkers (which only demonstrate progression of the cancer but not its molecular drivers), this could quite realistically result in an important new paradigm associated with solid tumor disease management.

In the current issue of *Oncology*, Lemech et al. [1] present a highly provocative preliminary report of the presence and characterization at the molecular level of circu-

lating tumor cells in women with advanced endometrial cancer. While the sample size was small ($n = 30$), the majority of patients (60%) were found to have detectable circulating tumor cells. Further, and of even greater interest, the investigators were able to examine the cells for the presence of a specific molecular marker (stathmin).

While these results will need to be confirmed by others, and the therapeutic implications of this observation will need to be further characterized, the results provide reasonable hope that in the near future it will be possible to monitor the course of illness and therapy in women with advanced endometrial cancer by examining for the presence or absence of circulating cancer cells, and for the existence of unique molecular findings.

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Reference

- 1 Lemech CR, Ensell L, Paterson JC, et al: Enumeration and molecular characterization of circulating tumour cells in endometrial cancer. *Oncology* 2016, DOI: 10.1159/000445999.