Monitoring response to therapy in patients with cancer: is circulating DNA the answer?

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Submitted May 14, 2013. Accepted for publication Jul 12, 2013.
doi: 10.3978/j.issn.2305-5839.2013.07.02
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One of the most frequent uses of tumor markers is in monitoring response to therapy in patients with advanced malignancy. Although serial imaging is the gold standard method for assessing response, the use of circulating markers has several advantages including non-invasive measurement, relatively low costs and convenience for patients. Proposed markers for monitoring therapy in patients with breast cancer include CA 15-3, CEA, TPA, TPS and circulating tumor cells (CTC) (1,2). Although the best marker for monitoring remains to be determined, CA 15-3 is the most widely used in clinical practice.

Recently, Dawson *et al.* (3) described the use of circulating tumor-derived DNA for monitoring response to therapy in 52 patients with advanced breast cancer. The circulating DNA measured was mostly derived from 2 mutant genes in the patients' tumors, i.e., from PIK3CA and TP53 (p53). Circulating tumor-derived DNA was compared with CA 15-3 and CTC. Although 52 patients were recruited, only 30 had identifiable tumor-related genetic alterations suitable for monitoring. Of these 30, 29 (97%) of the patients had detectable alterations in the circulation. In contrast, CTC were present in 26/30 (87%) and elevated levels of CA 15-3 in 21/27 (78%). Furthermore, serum DNA and CTC but not CA 15-3 were found to be prognostic of outcome.

The authors concluded that serum measurement of tumor-derived DNA showed a greater dynamic range and better correlation with alterations in tumor mass compared with CTC or CA 15-3. In addition, serum DNA gave the earliest indication of response to treatment in 10/19 patients.

Oncologists involved in everyday clinical practice may ask the question, what is the practical relevance of this proof of concept study? In particular, they may ask if the measurement of circulating tumor DNA is ready for prime time (4)?

Although the measurement tumor-derived DNA in serum appears to have a number of advantages vis-à-vis existing markers, it also has a number of limitations. Thus, in the study of Dawson *et al.* (3), detectable circulating tumor DNA was only present in 29 of the 52 recruited patients. Most of this informative DNA was derived from the 2 most frequently mutated genes in breast cancer, i.e., PIK3CA and TP53 (5,6). It could be argued that if DNA from additional mutant genes was evaluated, sensitivity could be increased. However, apart from PIK3CA and TP53, other genes in breast cancers appear to be mutated in less than 10% of cases (5,6). A further caveat is that determining gene mutation status is relatively expensive and time consuming and would not be practical in most diagnostic laboratories at present.

There may however, be specific situations in which measurement of tumor derived-DNA will provide information that is not available from the existing markers. Thus, preliminary findings suggest that mutations in PIK3CA genes result in resistance to trastuzumab (7,8). Detecting these mutations in a readily available fluid such as blood might thus be able to provide a non-invasive and early indication of resistance to this therapeutic antibody. In this context, it should be noted mutant KRAS DNA was recently found in blood from patients with advanced colorectal cancer that developed resistance to the anti-EGFR monoclonal antibody, panitumumab (9). In 3 of 9 patients, the mutated DNA was identified prior to

radiological evidence of disease progression.

Early detection of therapy resistance mutations via a non-invasive method, as found in this study (9) could lead to prompt cessation of an ongoing ineffective treatment and result in the administration of a new drug which might be more efficacious. Of course these preliminary finding with circulating tumor DNA in breast and colorectal cancer require confirmation before this technology can be recommended for prime time.

For now and for the short term, oncologist will therefore have to rely on the existing markers for monitoring therapy in patients with cancer, including breast cancer. Research into circulating tumor DNA should be continued. Provided the findings of Dawson *et al.* (3) can be confirmed in larger studies, these assays should be simplified and made available in a relatively inexpensive and convenient-to-use format.

Acknowledgements

The authors wish to thank Science Foundation Ireland, Strategic Research Cluster Award (08/SRC/B1410) to Molecular Therapeutics for Cancer Ireland, and the Irish Cancer Society BREAST CANCER PREDICT programme, for funding their work.
Disclosure: The authors declare no conflict of interest.

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Cite this article as: Duffy MJ, Crown J. Monitoring response to therapy in patients with cancer: is circulating DNA the answer? Ann Transl Med 2013;1(3):24. doi: 10.3978/j.issn.2305-5839.2013.07.02

