

Is “liquid biopsy” useful for assessing HER2 status in gastric cancer?

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After a delay of several years from its introduction to treat breast cancer, anti-HER2 monoclonal antibody (trastuzumab) combined with chemotherapy was proposed as a standard option for HER2-positive patients with advanced and/or recurrent gastric cancer [1]. Although immunohistochemical analysis of tumor tissues takes first priority for selecting patients, the “heterogeneity” of HER2 expression and/or difficulties in biopsy are frequent limitations, particularly for recurrent gastric cancer. Therefore, multiple biopsies are required to evaluate the precise status of HER2 expression [2, 3].

A “liquid biopsy” using blood is useful for characterizing circulating tumor cells instead of biopsies of tumor tissues [4], and serum biomarkers of gastrointestinal tumors provide convenient tools to assess tumor phenotypes [5]. For example, a recent extensive survey of the literature suggests that serum markers such as CEA, CA19-9, and CA72-4 facilitate staging of gastric cancers before surgery or chemotherapy and for assessing response to therapy and the risk of recurrence [6]. Moreover, serum biomarkers such as HER2 ECD may overcome the problem of heterogeneity of HER2 expression in tumor tissues. A systematic review of 63 studies of breast cancer conducted by Leyland-Jones et al. [7] revealed that HER2 ECD expression was significantly associated with the HER2 status of tumors. However, the serum HER2 ECD levels were not consistently related to patients’ outcomes.

Furthermore, the authors noted that 13 different assay techniques using 15 different cut-off values may explain the discrepant results. The results of four studies of gastric cancer are inconsistent regarding the associations among serum HER2 ECD levels, tissue HER2 expression status, and patients’ responses to treatment and their outcomes [8–11]. Similar to the results of these breast cancer studies, different cut-off values were used to define positive rates [11]. Because there is only limited data on the serum HER2 ECD levels in gastric cancer patients, it will be necessary to conduct more studies. Moreover, chemiluminescent immunoassays (CLIAs) [12] show promise as alternatives to enzyme-linked immunosorbent assays (ELISAs) for accurately assessing the HER2 status of tumors.

In recent issues of the *Journal of Gastroenterology*, Oyama et al. [13], using a highly sensitive CLIA, reported their evaluation of the clinical utility of using serum HER2 ECD levels in a study of 150 gastric cancer patients. Analysis of 36 patients before and after chemotherapy revealed significant associations between serum HER2 ECD and tissue HER2 expression levels, leading them to conclude that serum HER2 ECD levels predict tissue HER2 expression and therefore show promise for monitoring patients’ response to treatment. Although the low sensitivity (36.0 %) of serum HER2 ECD levels for detecting tissue HER2 expression may limit its use, it is excellent for monitoring the response to treatment. Because treatment with trastuzumab may interfere with the conventional ELISA [12], CLIA shows promise as an alternative. Thus, Oyama et al. established for the first time that a “liquid biopsy” to detect HER2 expression in tumors shows promise for monitoring the response to treatment of advanced/recurrent gastric cancer patients.

Zhang et al. [14] reported that an assay based on linear ribonucleic acid (RNA) fluorescent amplification catalyzed

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by T7 RNA polymerase technology is more sensitive compared with other methods. The studies described here lead one to the reasonable conclusion that a liquid biopsy to detect gastric carcinoma could be developed to improve the quality of monitoring of this disease and predicting its treatment response. What will be the next target of a liquid biopsy for gastric cancer? The malignant potential of gastric cancer is frequently attributed to high levels of angiogenic factors and/or growth factor expression rather than those of HER2 expression. Examples include vascular endothelial growth factor, fibroblast growth factor, and thymidine phosphorylase [15]. These molecules, as well as their receptors, may serve as potential targets of liquid biopsy assays for selecting the most appropriate treatment for gastric cancer patients.

Conflict of interest There is no conflict of interest regarding this manuscript.

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