Editorial

Detection of circulating tumor cells in gastrointestinal cancer: Has its time come?

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J Gastrointest Oncol 2012;3(2):84-85. DOI: 10.3978/j.issn.2078-6891.2012.014

Since the first report in the 19th century, there have been numerous reports on the isolation and characterization of circulating tumor cells (CTCs) in peripheral blood in patients with various cancers (1-3). Recent studies have shown that the malignant characteristics of CTCs are genetically similar to the primary tumor (4,5). However, their characterization is of considerable biomedical interest in order to understand how these cells can travel via the blood stream to anatomically distant sites and form metastatic disease. There have been many investigations which showed the utility of CTCs in the peripheral blood as a valuable diagnostic tool or a predictor of the clinical outcome in patients with solid tumors (2,3).

In general, CTCs have been observed in the peripheral blood of cancer patients at very low concentrations of 10^{-7}-10^{-8} of normal peripheral blood cells (6,7). Therefore, the detection of CTCs in blood requires highly sensitive, specific, and reproducible methods. To date, several methods including immunocytochemistry, reverse-transcription polymerase chain reaction (RT-PCR) or PCR procedures, and flow cytometry have been used for the detection of these rare CTCs in the peripheral blood (2,3,7,8). Moreover the CTC-detection systems using the immunobead-based assays during the past ten years were designed to detect tumor cells in blood (9). By use of these systems, it is possible to obtain highly reproducible quantitative results. In particular, recently developed CellSearch System (Veridex LLC, Raritan, NJ) was designed to quantify the tumor cells in whole blood (9). CTCs can be isolated and enumerated reproducibly and quantitatively in patients with metastatic cancer by immunomagnetic separation targeting the epithelial-cell adhesion molecule (EpCAM) in the CellSearch System. The CellSearch System was approved by the U.S. Food and Drug Administration for the detection of CTCs in the peripheral blood of patients with metastatic breast, colon and prostate cancer (10).

There have been several studies which investigated the prognostic value of CTC detection using the CellSearch System in patients with gastrointestinal cancers. Cohen *et al*. reported that clinical significance of CTCs in 430 patients with metastatic colorectal cancer at baseline and after starting first-, second-, or third-line therapy in a prospective multicenter study using the CellSearch System (11). As results, patients with ≥3 CTCs per 7.5 mL of the blood at baseline had a significantly worse progression-free survival (PFS) and overall survival (OS) compared with the patients with <3 CTCs at baseline of pretreatment metastatic colorectal cancer. Interestingly, conversion of baseline ≥3 CTCs to <3 CTCs at 3 to 5 weeks was associated with significantly longer PFS and OS compared with patients with ≥3 CTCs at both time points. Baseline and follow-up CTC levels remained strong predictors of PFS and OS after adjustment for clinically significant factors. They concluded that CTCs can provide significant prognostic information prior to that of imaging studies.

Hiraiwa *et al*. (12) in a study carried out in our department evaluated CTCs in 130 patients with gastrointestinal cancers including 44 gastric, 48 colorectal, and 38 esophageal cancers, using the CellSearch System and clarified the clinicopathologic characteristics of CTCs. As results, CTC counts were significantly larger in metastatic gastric cancer than in nonmetastatic gastric cancer or healthy donors. The survival of patients with ≥2 CTCs was significantly shorter than that of patients with <2 CTCs. Moreover the change in CTCs tended to correlate with disease progression

No potential conflict of interest.

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Submitted Mar 07, 2012. Accepted for publication Mar 14, 2012.
Available at www.thejgo.org

ISSN: 2078-6891

and chemotherapeutic effect. These studies suggest that measurement of CTCs in gastrointestinal cancer patients could be useful as a promising tool for judging tumor stage, predicting the distant metastasis and patients' survival, and monitoring response to cancer therapy.

Although detection of CTCs has also been evaluated in several studies to predict the poor prognosis or monitor chemotherapy outcomes in pancreatic cancer (13-15), clinical significance of CTCs in biliary cancers still remains unclear. The current article by Ustwani *et al*. (16) reports on the detection of CTCs using the CellSearch System in 16 patients with cholangiocarcinoma or gallbladder cancer for the first time. In their pilot study using a cutoff of 2 CTCs per 7.5 mL, 25% of patients with biliary cancer had detectable CTCs. As results, only 25% of patients with positive CTC were alive while 50% of patients with negative CTC remained alive at 12 months of follow up from time CTC is drawn. Although the difference in survival between the two groups did not reach a statistical significance because of the shortage of the sample size, the article might represent a valuable signpost for the future direction of the CTCs in biliary cancers.

Molecular characteristics and biological behaviors of CTCs are extremely attractive for researchers to elucidate how these cells can metastasize from primary tumors (7). Further studies might disclose the molecular characterization of cancer stem cells which can metastasize easily and are captured as CTCs in the peripheral blood. Moreover assessment of cancer stem cells through CTC research can provide the rational design of targeted anticancer therapies.

Detection and measurement of CTC would become a promising tool as prognostic, predictive, and diagnostic markers for patients with gastrointestinal cancers. To achieve this goal, the clinical relevance should be verified in large-scale clinical trials. However, CTC detection will surely provide abundant useful information to the tumor staging and anticancer treatments in clinical practices for patients with gastrointestinal cancers in near future.

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Cite this article as: Takeuchi H, Kitagawa Y. Detection of circulating tumor cells in gastrointestinal cancer: Has its time come? J Gastrointest Oncol 2012;3(2):84-85. DOI: 10.3978/j.issn.2078-6891.2012.014