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Editorial

Epigenetics modulates the effect of chemotherapy on gastric cancer

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The significance of aberrant *CHFR* methylation for clinical response to microtubule inhibitors in gastric cancer
Koga Y, Kitajima Y, Miyoshi A, et al.

Gastric cancer is the most commonly diagnosed type of cancer in the world,[1,2] and this disease still has a high prevalence rate and morbidity in Japan. Although many randomized chemotherapy trials for metastatic gastric cancer have been reported during the past two decades, to date no standard regimens have been established worldwide. In Europe, a combination of fluorouracil, doxorubicin, and high-dose methotrexate (FAMTEX) used to be the standard regimen, based on the European Organization for Research and Treatment of Cancer (EORTC) trials.[3] However, this regimen failed to demonstrate any superiority over other combination regimens in subsequent EORTC trials, for example, versus 5-fluorouracil (5-FU) plus cisplatin or etoposide plus a 5-FU/leucovorin combination in a randomized study.[4] The results of these randomized trials suggest that cisplatin (CDDP) plus 5-FU (CF) could be a reasonable reference arm. However, even this regimen has not shown superiority to 5-FU alone in terms of overall survival, and its efficacy is still limited compared with that of older generation regimens: the response rates ranged from 10% to 35%, and the median survival time (MST) was from 6 to 8 months, with around 10% surviving 2 years. To overcome these limitations, new active agents are essential.

Recently in Japan, S-1 and taxanes have begun to attract attention. S-1 is a new oral fluoropyrimidine consisting of three components: tegafur (FT), which is a prodrug of 5-FU; 5-chloro-2,4-dihydroxypyridine (CDHP), which competes with dihydropyrimidine dehydrogenase; and oxonic acid (Oxo). When given at a molar ratio of 1:0.4:1, the gastrointestinal toxicity of tegafur is suppressed. Various trials of S-1 in combination with other agents such as CDDP, irinotecan, and taxanes have been conducted, particularly in Japan. At first, S-1 was combined with CDDP.[5] This study (JCOG9205) revealed an excellent response rate of 76% with an MST of 12.6 months. Based on the results of, the Japan Clinical Oncology Group (JCOG) chose the single agent 5-FU as the reference arm and has initiated three-arm randomizations (JCOG9912), in which 5-FU alone is compared with a combination of irinotecan/CDDP and with S-1 alone.[6] Great hopes ride on the results of that study.

The taxanes docetaxel and paclitaxel inhibit microtubule depolymerization and have moderate activity against gastric cancer, with a response rate of around 20% in single-agent studies. Paclitaxel was combined with a CF regimen in a Korean phase II study,[7] and the Swiss Group for Clinical Cancer Research has reported a phase II study of docetaxel with CDDP.[8] Recently, taxanes have been reported to be effective against gastric cancer as second line chemotherapy.[9,10]

Much about the genetic and epigenetic abnormalities involved in gastric tumorigenesis remains unknown.[11,12] Epigenetic changes such as DNA methylation are known to be involved in the inactivation of tumor suppressor genes;[13,14] indeed, such aberrant methylation has been detected frequently in gastric cancer.[15–17] In addition, DNA methylation of multiple CpG islands has been detected in a subset of gastric cancers that appear to have the CpG island methylator phenotype, which causes most cases of sporadic gastric cancers with microsatellite instability, followed by *hMLH1* methylation.[16,18,19]

CHFR [checkpoint with forkhead-associated (FHA) and ring finger] encodes a protein with FHA and RING finger domains that functions in the mitotic checkpoint pathway, which governs the transition from prophase to prometaphase.[20,21] Expression of this gene is apparently lost in several human cancer cell lines and primary lung and esophageal cancers.[20,22,23] Cell-cycle checkpoint dysfunction is often associated with sensitivity to chemotherapeutic agents. Satoh et al.[24] have demonstrated that microtubule inhibitors such as docetaxel and

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Reprint requests to: F. Itoh

paclitaxel induce apoptosis in gastric cancer cell lines with *CHFR* methylation. Moreover, they found that gastric cancer cell lines not expressing CHFR lack a mitotic checkpoint and are highly susceptible to microtubule inhibitors. Thus, Satoh et al.[24] suggest that DNA methylation of *CHFR* may be a useful molecular marker by which to predict the responsiveness of gastric cancers to treatment with microtubule inhibitors. However, for several years, no results regarding *CHFR* in primary gastric cancer cases, especially with respect to microtubule inhibitor effectiveness, have been reported. In this issue of the *Journal of Gastroenterology*, Koga et al.[25] report a novel aberrant *CHFR* methylation in the clinical response to microtubule inhibitors in primary gastric cancer cases. According to their report, assessment of the *CHFR* methylation status may be clinically useful for predicting the response of gastric cancers to treatment with microtubule inhibitors. This report will bring *CHFR* gene methylation closer to clinical application as a molecular marker.

Yoshiyuki Watanabe, M.D., Ph.D.,
and Fumio Itoh, M.D., Ph.D.
Division of Gastroenterology and Hepatology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan

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