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*Mini Review*

# Overview of factors associated with the effectiveness of tegafur-uracil treatment

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**Pyrimidine fluoride anticancer drugs are used for the treatment of various cancers, such as lung cancer, colorectal cancer, gastric cancer, and breast cancer. In particular, tegafur-uracil treatment is well established as a postoperative adjuvant chemotherapy for Non-Small Cell Lung Cancer (NSCLC) patients, although the effectiveness of treatment differs depending on the type of cancer cells and the state of progression. Some characteristics of cancer cells may be associated with their treatment responses to tegafur-uracil. First, the genomic profiles of cancer cells may affect their response to tegafur-uracil therapy, although it remains unclear as to what specific genomic profiles of NSCLCs are associated with favorable treatment outcomes. Second, the tumor microenvironment that is created by the unique metabolic characteristics of cancer cells and is known to be associated with cancer progression and drug resistance may also be associated with the treatment response to tegafur-uracil. However, further studies are required to clarify the specific factors that are associated with the treatment response of cancer cells to tegafur-uracil.**

**Key words:** Tegafur-uracil, colorectal cancer, breast cancer, genomic profiling, tumor microenvironment

## INTRODUCTION

Tegafur-uracil, a pyrimidine fluoride anticancer drug, has been recommended as postoperative adjuvant chemotherapy for Non-Small Cell Lung Cancer (NSCLC) patients for the previous two decades. One of our authors, Wada et al., conducted a randomized comparative study of cisplatin + vindesine + tegafur-uracil therapy, tegafur-uracil monotherapy, and surgery alone in pathologic stage I to III NSCLC patients after complete resection. The 5-year survival rates were 60.6% for the cisplatin + vindesine+ tegafur-uracil therapy group, 64.1% for the tegafur-uracil monotherapy group, and 49.0% for the surgery alone group, demonstrating in particular that the 5-year survival rate of the tegafur-uracil monotherapy group was significantly higher than that of the surgery alone group (Wada H et al., 1996). Subsequently, several follow-up clinical trials to investigate the effect of tegafur-uracil as an adjuvant chemotherapy after surgery for NSCLC were conducted, and a meta-analysis of 6 randomized control studies (2003 patients; 84% adenocarcinoma, 16% non adenocarcinoma) showed that tegafur-uracil as an adjuvant chemotherapy after surgery significantly improved the 5-year and 7-year survival rates of patients (Kato H et al., 2004, Hamada C et al., 2005). In particular, for pathologic stage IA (7th edition of the TNM classification) lung adenocarcinoma patients with a tumor size of more than 2 cm and 3 cm or less, who were treated with surgery + tegafur-uracil, the 5-year survival rate was higher (88%) than in patients treated with surgery only (82%). On the other hand, for pathologic stage IA (7th edition of the TNM classification) lung adenocarcinoma patients with a tumor size of 2 cm or less, the 5-year survival rate did not differ significantly between surgery +tegafur-uracil (87%) and surgery alone (85%) (Hamada C et al., 2009). A retrospective study to investigate the effectiveness of tegafur-uracil as an adjuvant chemotherapy in pathologic stage IB (7th edition of the TNM classification) NSCLC patients with a primary tumor size of more than 3.0 cm and 5.0 cm or less showed that the tegafur-uracil group had a tendency to achieve more favorable outcomes than the surgery alone group (Adachi H et al., 2019). Moreover, for pathologic stage IA (7th edition of the TNM classification) NSCLC patients with lymph vascular invasion, which is thought to be associated with an unfavorable prognosis, a single-arm phase 2 study showed that postoperative adjuvant chemotherapy with tegafur-uracil might potentially improve postoperative outcomes (Tsuchiya T et al., 2020). Therefore, tegafur-uracil is recommended as postoperative adjuvant chemotherapy for pathologic stage IA/IB/IIA NSCLC patients (a tumor size of more than 2 cm and

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5 cm or less, by the 8th edition of the TNM classification) who underwent complete resection of the tumor.

## LITERATURE REVIEW

Pyrimidine fluoride anticancer drugs are used for various cancers, such as colorectal cancer, gastric cancer, and breast cancer. However, the effects of these drugs differ between cancers. For clinical stage III colon cancer patients, combination therapy of a pyrimidine fluoride anticancer drug and oxaliplatin is the standard adjuvant chemotherapy after surgery. Oral pyrimidine fluoride anticancer drugs, such as tegafur-uracil + leucovorin, fluorouracil + levoleucovorin, and S-1 + capecitabine are also considered to be treatment options for oral adjuvant chemotherapy, because of the high frequency of adverse events associated with combination therapies using oxaliplatin, such as hematotoxicity and peripheral neuropathy (Shimada Y et al., 2014). The treatment results of postoperative adjuvant chemotherapy by pyrimidine fluoride monotherapy in Japanese patients with stage III colon cancer were reported to be more favorable than in studies performed in the US and Europe (Kusumoto T et al., 2018). Moreover, for stage III rectal cancer patients, it was reported that tegafur-uracil monotherapy is superior to surgery alone regarding recurrence-free survival after surgery, although S-1 monotherapy was shown to be superior to tegafur-uracil monotherapy regarding recurrence-free survival after surgery in stage II/III rectal cancer patients (Oki E et al., 2016, Hamaguchi T et al., 2011). Therefore, oral pyrimidine fluoride anticancer drug monotherapy is considered to be optional postoperative adjuvant chemotherapy for colorectal cancer patients, which should be considered based on the risk-benefit balance, including adverse events and efficacy.

In gastric cancer patients, although S-1 or capecitabine is used as a fluoropyrimidine anticancer drug, tegafur-uracil is not used. For stage II or III gastric cancer patients who underwent D2 gastrectomy, S-1 monotherapy is recommended as a postoperative adjuvant chemotherapy; on the other hand, for stage III gastric cancer patients, S-1 monotherapy or combination therapy of oxaliplatin + capecitabine may be considered as a treatment option depending on the risk-benefit balance for each patient (Sasako M et al., 2011, Takahari D et al., 2011).

For breast cancer patients, oral pyrimidine fluoride anticancer drugs, including tegafur-uracil, are thought to be superior to intravenous chemotherapies in terms of the patients' quality of life during treatment; however, clinal trials showed that the overall survival and disease-free survival of patients treated with oral pyrimidine fluoride as a postoperative chemotherapy tended to be less favorable than those who received intravenous chemotherapy (doxorubicin/cyclophosphamide, or cyclophosphamide/methotrexate/5-fluorouracil) (Shien T et al., 2014). Moreover, the effectiveness of the currently used chemotherapy regimens, such as the sequential administration of anthracyclines to taxanes or docetaxel + cyclophosphamide, has not been compared with the effectiveness of oral pyrimidine fluoride anticancer drugs. Therefore, for breast cancer patients, the currently used intravenous chemotherapy regimens are more frequently recommended as adjuvant chemotherapy after surgery than oral pyrimidine fluoride anticancer drugs.

Taken together, although pyrimidine fluoride anticancer drugs are used for the treatment of a variety of cancers, tegafur-uracil is not a first-line option as a postoperative adjuvant therapy for patients with cancers other than NSCLC, and treatment responses to tegafur-uracil depend on the cancer type.

## DISCUSSION

Pyrimidine fluoride anticancer drugs, such as tegafur-uracil, have different therapeutic responses depending on the type of cancer, and are usually recommended for use as adjuvant chemotherapy, that is, for the prevention of recurrence rather than for the treatment of patients with advanced stages of disease, i.e., those with aggressive disease. Therefore, some characteristics of cancer cells may be associated with their treatment responses to pyrimidine fluoride anticancer drugs.

First, the genomic profile of cancer cells is thought to be associated with cancer progression and their treatment responses to chemotherapeutic drugs. For NSCLC patients who have driver-gene mutations/translocations, such as the *EGFR* mutation, *ALK* fusion gene, *ROS1* fusion gene, *BRAF* mutation, and *MET* mutation, therapeutic target drugs for each genetic abnormality are predicted to be effective and are recommended (Kris MG et al., 2014). Somatic mutations in other genes, such as *KRAS*, *HER2*, *PIK3CA*, and *DDR2* have also been considered as potential targets for genotype-based treatment approaches against NSCLC (Pao W et al., 2011). Multiplex genotyping for 214 somatic hotspot mutations in 26 genes, 20 major variants of *ALK*, *RET*, and *ROS1* fusion genes, and the evaluation of MET amplification by fluorescence in situ hybridization were conducted using archival formalin-fixed, paraffin-embedded tumor specimens from a phase III trial comparing first-line S-1 + carboplatin with paclitaxel + carboplatin in patients with advanced NSCLC. It was reported that a somatic mutation in at least one gene, such as *EGFR* (17%), *TP53* (11%), *STK11* (9.8%), *MET* (7.6%), and *KRAS* (6.2%) was identified in 48% of non-squamous cell carcinoma and 45% of squamous cell carcinoma specimens. Moreover, *ALK* fusion (2.5%), ROS1 fusion (2.1%), *RET* fusion (0.4%), and *MET* amplification (3.9%) were also identified in the specimens, and *KRAS* mutations were associated with a shorter median survival of patients (Okamoto I et al., 2014). Recently, it was reported that *EGFR*-mutant lung cancer cells expressing high levels of protein AXL do not respond well to the *EGFR*-tyrosine kinase inhibitor osimertinib, because AXL enhances the survival signal and is associated with resistance to treatment (Taniguchi H et al., 2019). Moreover, in *EGFR*-mutant lung cancer cells with low AXL expression, an increased level of insulin-like growth factor-1 receptor caused by the transcription factor FOXA1 is reported to induce drug resistance (Wang R et al., 2020). Although the genetic diversity of NSCLCs may also affect their response to cytotoxic chemotherapeutic agents, including pyrimidine fluoride anticancer drugs, it remains unclear as to what genetic profiles of NSCLC are associated with favorable treatment outcomes.

Second, cancer cells are known to have unique metabolic characteristics compared with normal cells, and they create a tumor microenvironment that is associated with cancer progression and drug resistance (Harguindey S et al., 2005).

Normal cells usually produce Adenosine Tri Phosphate (ATP) via oxidative phosphorylation, whereas cancer cells produce ATP via high rates of aerobic glycolysis to support their rapid cell cycle (Warburg effect) (Gatenby RA et al., 2004). Many researchers have demonstrated that the pH of the tumor microenvironment, which is regulated by acid-base transporters, such as $Na^+/H^+$ exchangers and mono carboxylate transporters, is acidic owing to proton accumulation caused by lactic acid production through the Warburg effect (Harguindey S et al., 2005, Cairns RA et al., 2011). The activated $Na^+/H^+$ exchanger is suggested to contribute to intracellular alkalization and extracellular acidosis, which affects tumor proliferation and progression, and is also reported to activate cofilin-1, which is involved in actin cytoskeleton signaling and plays a key role in cancer cell migration (Amith SR et al., 2013). An *in vitro* study of human lung cancer cells demonstrated that an increase in intracellular pH to 7.4 compared with 7.0 results in a nearly 2,000-fold increase in adriamycin resistance (Harguindey S et al., 2005). Therefore, altering pH homeostasis in and around the tumor microenvironment may affect treatment responses to oral pyrimidine fluoride anticancer drugs, such as tegafur-uracil.

## CONCLUSION

Although tegafur-uracil treatment is well established for NSCLC patients as a postoperative adjuvant chemotherapy, its effectiveness differs depending on the type of cancer cell and the state of progression. The genomic profile of cancer cells and the tumor microenvironment may be associated with treatment outcomes, although further studies are needed to clarify these points.


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## CONFLICTS of INTEREST

The authors declare that they have no conflicts of interest associated with this study.

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