Effects and Mechanisms of Trifluridine alone or in Combination with Cryptotanshinone in Inhibiting Malignant Biological Behavior of Gastric Cancer

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Abstract

Background: Gastric Cancer (GC) is the fourth most common malignant tumor worldwide. This study aimed to investigate the effect of a combination of Cryptotanshinone (CTS) and Trifuorothymidine (FTD) on GC.

Methods: The efect of the combined or separate use of FTD and CTS on HGC-27 and AGS cells was detected using the CCK8 assay. The combined index of FTD and CTS was calculated using Compusyn software. Additionally, we apploM

efect of TAS-102 in combination with CTS was studied in a xenograft nude mouse model.

Results: FTD and CTS inhibited the prolifActivator of Transcription 3) phosphorylation, whereas CTS downregulated p-STAT3. Interest CTS and FTD reduced the STAT3 phosphorylation induced by FTD. In vivo, the combination of TAS-102 with CTS was significantly more potent than TAS-102 alone in tumor growth inhibition.

Conclusions: FTD combined with CTS has a synergistic anti-gastric cancer effect in vitro and in vivo and is a promising treatment option for advanced GC.

Keywords: Tri uorothymidine; Cryptotanshinone; Gastric cancer;

combination with other chemotherapeutic agents. TAS-102 is a combination of a novel oral nucleoside analog tri uorouracil (FTD) and thymine phosphorylase inhibitor tipilasi hydrochloride (TPI) in a molar ratio of 1:0.5. FTD is the active cytotoxic component of TAS-102, and TPI plays a role in prevent rapid degradation and inactivation of FTD by thymine phosphorylase in vivo. FTD enters the body via nucleoside transporters and is sequentially phosphorylated by thymidylate kinase. Its monophosphate-phosphate form (FTD-MP) can temporarily inhibit thymic acid synthase (TS) and its triphosphate form (FTD-TP) can be inserted into DNA strands [4]. TS inhibition is the main mechanism of action of classical uoropyridines such as 5-FU. Although the inhibition of TS by FTD-MP may partially explain the anti-tumor e ect of FTD, studies have shown that the incorporation of FTD-TP into the DNA chain, resulting in DNA damage, is the

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subsequently incubated with the speci c primary antibody at 4°C overnight. GAPDH or -actin served as internal controls. e next day, the membranes were washed three times with TBST (Tris-bu ered saline and 0.1% Tween-20) and incubated at room temperature for 1h with the corresponding secondary antibody. Each band was examined by adding chemiluminescence (ermo Scienti c) toed

rates. However, Traditional Chinese medicine has great potential in the treatment of advanced gastric cancer owing to its advantages of improving patients' quality of life, low toxicity, side reactions, and sensitization chemotherapy. erefore, understanding the e ect and mechanism of the combination of FTD and CTS in gastric cancer treatment is of great importance to doctors. Our results are the rst to reveal the *in vitro* and *in vivo* combinational e ects of FTD and CTS in gastric cancer.

Chemotherapy is the primary method of comprehensive multidisciplinary treatment for advanced gastric cancer. recommended rst-line chemotherapy regimen for gastric cancer includes oxaliplatin combined with uorouracil (FOLFOX or XELOX), docetaxel/paclitaxel combined with cisplatin (TP), and irinotecan combined with uorouracil (FOLFIRI), but its e cacy has not been satisfactory. As a novel uorouracil anti-tumor agent, TAS-102 was rst approved in Japan in 2014 for the treatment of unresectable advanced or recurrent colorectal cancer [15]. e study of TAS-102 in patients with gastric cancer began with a phase 3 trial in a large sample (n=507) of patients with metastatic or advanced gastric cancer in Eastern and Western countries who had received at least two previous chemotherapy treatments. e results showed a 31% reduction in the risk of death in the TAS-102 group compared with that in the placebo group. Based on this study, TAS-102 was recently approved by the Food and Drug Administration (FDA) for gastric or gastroesophageal junction adenocarcinoma in patients who had previously received at least two chemotherapy regimens, including uorouracil, platinum compounds, taxane, and irinotecan [11]. Here, our results demonstrate that FTD and CTS combined treatment of gastric cancer cells had signi cantly stronger inhibition of proliferation than each single drug treatment group. More importantly, the two drugs showed synergistic anticancer e ects at appropriate concentrations. Previous studies have shown that TAS-102 may enhance the e cacy of combination therapy with the chemotherapy agents irinotecan, oxaliplatin, and the targeted chemotherapeutic agent bevacizumab.

We further analyzed the potential mechanism of the synergistic e ect of FTD and CTS on the cell cycle and apoptosis. Compared with the control group, CTS alone blocked HGC-27 cells in the G1 phase and signi cantly reduced Cyclin D1 levels, which was consistent with our previous ndings. FTD blocks cells in G2 phase and upregulates Cyclin B1 expression. A er combining FTD and CTS, we found that the cells were mainly block HGC-27 cells at the G2 phase, and the expression level of mitotic phosphoprotein monoclonal antibody(MPM)-2

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Contributions

PQL, LXZ, and ZMC performed the experiments, conducted the statistical analysis, and dra ed the manuscript. GW assisted in performing the experiments. HZ and SCY discussed the results and helped revise the manuscript. AMX, WXH, and ZJW designed the main study and critically revised the manuscript. All authors have read and approved the nal manuscript.

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