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MINIREVIEWS

Proton pump inhibitor: The dual role in gastric cancer

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Abstract

Proton pump inhibitors (PPIs) are one of the most frequently used medications for upper gastrointestinal diseases. However, a number of physicians have raised concern about the serious side effects of long-term use of PPIs, including the development of gastric cancer. Recent epidemiological studies have reported a significant association between long-term PPI intake and the risk of gastric cancer, even after successful *Helicobacter pylori* eradication. However, the effects of PPIs on the development of pre-malignant conditions such as atrophic gastritis or intestinal metaplasia are not fully known, suggesting the need for comprehensive and confirmative studies are needed in the future. Meanwhile, several experimental studies have demonstrated the effects of PPIs in reducing chemoresistance in gastric cancer cells by modulating the acidic microenvironment, cancer stemness and signal transducer and activator of transcription 3 (STAT3) signaling pathway. The inhibitory effects of PPIs on STAT3 activity may overcome drug resistance and enhance the efficacy of conventional or targeted chemotherapeutic agents. Taken together, PPIs may "play dual role" in gastric carcinogenesis and treatment of gastric cancer.

Key words: Proton pump inhibitor; Gastric cancer; Drug resistance; Signal transducer and activator of transcription 3

Core tip: Recent epidemiological studies have demonstrated a significant increase in gastric cancer risk following the long-term use of proton pump inhibitors (PPIs). However, observational studies have fundamental limitations. PPIs may affect gastric cancer cells and the microenvironment by modifying the acidic conditions and inhibiting the cancer stemness *via* various signaling pathways including signal transducer and

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activator of transcription 3, which in turn, reduces drug resistance to chemotherapy. In this review, we briefly summarize the current clinical outcomes of the effects of long-term PPI use and the development of gastric cancer, as well as experimental studies showing enhanced chemosensitivity in gastric cancer.

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INTRODUCTION

Gastric cancer is one of the most frequently found malignant solid tumors worldwide, and is the third leading cancer-related cause of mortality[1]. Advances in technical and clinical knowledge have increased the early detection of gastric cancer for prompt intervention and successful management[2]. However, a significant number of gastric cancer cases are still diagnosed in advanced stages with distant metastasis, resulting in poor prognosis. A recent pivotal prospective randomized study showed that the overall survival in gastric cancer with a single metastasis was not significantly different between patients receiving chemotherapy alone and patients treated with gastrectomy combined with chemotherapy. The study also reported that the median overall survival was less than 18 mo[3].

Significant risk factors for gastric cancer include male gender; old age; ethnicity; *Helicobacter pylori* (*H. pylori*) infection; dietary factors, such as smoked food, high salt intake, pickled vegetables and nitrated meat; smoking; and family history. In terms of gastric factors, atrophic gastritis and intestinal metaplasia are proven pre-cancerous conditions[4]. A South Korean study showed that the risk of developing gastric cancer was increased more than 10 fold among subjects who had intestinal metaplasia compared with subjects who did not[5]. Thus, avoidance and optimal surveillance of risk factors are mandatory for the prevention of gastric cancer.

Proton pump inhibitors (PPIs) are the most potent acid inhibitors ever developed: they act by blocking the H^+/K^+ ATPase of parietal cells[6]. PPIs are powerful acid inhibitors and there, are widely used as drugs of choice for the treatment of gastroesophageal reflux disease (GERD) and drug-induced peptic ulcers. Long-term use of PPIs may facilitate the optimal management of GERD combined with severe complications such as esophageal stricture[7], and in practice, the long-term prescription of a PPI is often preferred as maintenance therapy, even for uncomplicated GERD patients[7]. However, there are rising concerns about the potential side effects of long-term PPI intake which include *Clostridium difficile* infection, pneumonia, bone fractures, dementia, chronic renal disease and small intestinal bacterial overgrowth[8]. Recent observational studies demonstrated a positive association between PPI use and malignant or pre-malignant tumors of the gastrointestinal tract. Reflecting recent trends, a recent expert opinion suggests that the dose of long-term PPIs should be periodically re-evaluated and that the lowest possible effective dose needs to be prescribed[9]. However, several experimental studies showed significant anti-tumor effects of PPI in cancer cells such as Barrett's adenocarcinoma and melanoma cells[10,11], and suggested that PPIs may contribute to reducing of tumor resistance to chemotherapy[12]. Several experimental studies have demonstrated this "unexpected" effect of PPIs in gastric cancer cells. In this review, we focused on the dual action of PPIs in gastric cancer. We not only summarized the clinical outcomes correlating the development of gastric malignancy with long-term use of PPI but presented an experimental hypothesis and experimental evidence supporting the anti-tumorigenic, drug-sensitizing effects of PPI in gastric cancer cells.

PPI AND GASTRIC CARCINOGENESIS

Hypothesis for causality of PPI and gastric cancer

The most plausible hypothesis for the association between long-term PPI intake and the development of gastric cancer is mediated *via* hypergastrinemia due to the reduced secretion of gastric acid[13]. This reduced acidity, in turn, triggers a proliferation of enterochromaffin-like cells (ECL cells), which express gastric

cholecystokinin-2 (CCK-2) receptors and are the target cells of gastrin in the oxyntic mucosa, and formation of neuroendocrine tumors (NETs)[14]. The somatostatin-mediated negative feedback of gastrin release on antral G-cells is frequently inhibited by gastric hypochlorhydria caused by long-term PPI use and other anti-acidic drugs, which leads to hypergastrinemia and hyperplasia of the gastric mucosa or ECL-cells[15]. The second hypothesis is that gastrin *per se* has a trophic effect on the oxyntic mucosa, as well as on ECL cells, under hypergastrinemic conditions such as chronic atrophic gastritis or prolonged PPI use[16]. A previous animal study showed that a high salt diet administered to *H. pylori*-infected Mongolian gerbils significantly increased serum gastrin levels and mucosal inflammation, which were ameliorated by a gastrin antagonist[17]. A recent case-control study showed that the subgroup with the highest quartile of serum gastrin levels was significantly associated with gastric non-cardia adenocarcinoma [fully adjusted odds ratio (OR) = 1.92; 95% confidence interval (CI): 1.21-3.05], as well as NET (age-adjusted continuous model OR = 4.67; 95%CI: 2.67-8.15)[18].

However, a molecular link between ECL cell hyperplasia and gastric adenocarcinoma is less relevant than gastric NET in general[14]. Nevertheless, a fraction of gastric adenocarcinomas originates from ECL cells. A previous study using human gastric carcinoma tissues showed that ECL cell markers, such as chromogranin A, synaptophysin, histidine decarboxylase and neuron specific enolase, were predominantly expressed in diffuse type gastric cancer rather than intestinal type gastric cancer[19]. Moreover, several pathologic studies have shown that most periodic acid-Schiff (PAS)-positive signet ring cell carcinomas abundantly expressed ECL-cell markers, but not mucin, suggesting that signet ring cell carcinoma might be a consequence of dedifferentiation from ECL cells toward signet ring cells with PAS-positive cytoplasm[20,21]. At the present stage, the effect of PPIs might be summarized by the following statement. PPIs reduce gastric acid secretion and lead to hypergastrinemia with the proliferation of ECL cells in the oxyntic gland, partially and theoretically explaining the potential association between PPI and gastric cancer, or at least, the enhancement of *H. pylori*-associated gastric carcinogenesis[22] (Figure 1). However, this hypothesis is often insufficient to elucidate the mechanism of PPI-induced gastric carcinogenesis. Moreover, a recent pivotal translational study demonstrated that PPI-treated patients showed similar microbial diversity compared with normal subjects while patients with *H. pylori*-induced atrophic gastritis manifested a lower bacterial abundance and diversity. This finding suggested that PPIs do not significantly alter gastric microbiota nor do they contribute significantly to the development of gastric cancer[23].

Clinical evidence supporting the association of PPI and development of gastric cancer

Previously, three retrospective, case-control studies from databases of Western countries analyzed the increased risk of gastric cancer with PPI intake[24-26]. These studies included relatively small number of gastric cancer cases (approximately 2000) and missed several major confounding factors, such as *H. pylori* infection status, dietary patterns or family history of gastric cancer. A meta-analysis which included the above three case-control studies, showed that the pooled relative risk (RR) of gastric cancer following PPI use was 1.43 (95%CI: 1.23-1.66) using both fixed- and random-effects models. However, the subgroup analysis failed to show a dose-dependent relationship between PPI and gastric cancer (PPI < 12 mo: pooled RR = 1.73, 95%CI: 1.24-2.52; > 12 mo: pooled RR = 1.42, 95%CI: 0.98-2.07; > 36 mo: pooled RR = 2.45, 95%CI: 1.41-4.25). The authors stated that colonization with *H. pylori* and adequate long-term use of PPI synergistically increased the risk of gastric cancer[27]. Another previous meta-analysis showed a similar effect of acid suppressive drugs on gastric cancer (adjusted OR = 1.42; 95%CI: 1.29-1.56); however, the pooled effect was confounded by H2RA, and was not solely due to PPI[28].

Recently, Cheung *et al*[29] showed a positive correlation between PPI and gastric cancer in *H. pylori*- infected patients who underwent eradication therapy. In this large-scale, population-based study involving a Hong Kong health database, the authors enrolled more than 63000 adult patients who were prescribed with a clarithromycin-based triple therapy. Current *H. pylori* infection was diagnosed by an invasive or non-invasive study. To eliminate protopathic bias, patients who were diagnosed with gastric cancer within six months before the study or within 12 mo after *H. pylori* eradication therapy were excluded[30]. Furthermore, to minimize the effect of *H. pylori*-induced gastric carcinogenesis, only patients successfully treated with eradication therapy were enrolled. Failure of *H. pylori* eradication was therapy identified if patients were prescribed subsequent medication of (1) repeated standard triple therapy, (2) bismuth-containing second-line quadruple therapy, or (3) rifabutin-based third-line therapy. During a median follow-up of 7.6 years, 153 patients (0.24%)

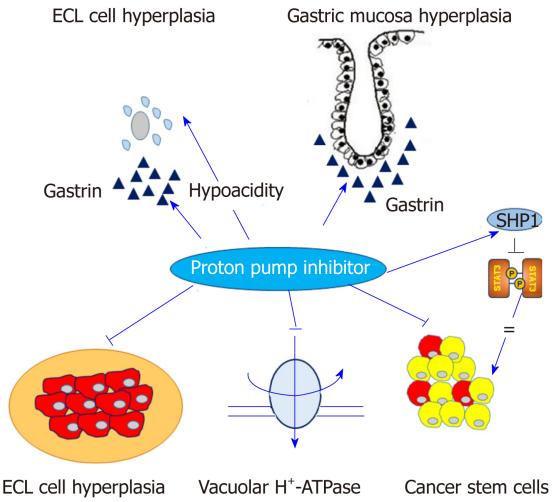

Figure 1 Contrast effects of proton pump inhibitors in normal gastric mucosa and gastric cancer cells. Proton pump inhibitors (PPIs) induce hypergastrinemia and hypochlorhydria, which may contribute to enterochromaffin-like cell hyperplasia and proliferation of gastric mucosa. Conversely, PPIs may modify the acidic tumor microenvironment and inhibit vacuolar H^+-ATPase or signal transducer and activator of transcription 3 activity in gastric cancer cells. Arrow indicates the positive effect and straight line indicates the inhibitory effect. ECL: Enterochromaffin-like; SHP1: Src homology 2 domain-containing protein tyrosine phosphatase 1; STAT3: Signal transducer and activator of transcription 3.

developed gastric cancer. PPI use significantly increased the risk of gastric cancer [hazard ratio (HR) = 2.44; 95%CI: 1.42-4.20], unlike H2RA (HR = 0.72; 95%CI: 0.48-1.07). Moreover, the positive association between PPI and gastric cancer showed dose- and duration-dependent relationship[29]. This study was significant in that it demonstrated the increased risk of gastric cancer with long-term use of PPIs, even after successful eradication of *H. pylori*. However, it had several important limitations. First, due to the fundamental limitations of observational studies, several baseline characteristics such as age, metabolic diseases (diabetes, hypertension, and dyslipidemia) and other major comorbidities (ischemic heart disease, stroke, congestive heart failure, and chronic renal failure) were significantly biased between the case and control groups. Consequently, gastric atrophy, salty food intake or obesity, which are related to gastric cancer development, may have occurred more frequently in the PPI user group, even after statistically sophisticated propensity-score matching[31]. Second, important confounding factors of gastric cancer such as gastric atrophy, intestinal metaplasia and dietary patterns were excluded[32]. Third, the authors determined success or failure of *H. pylori* eradication only based on prescription histories. Thus, a portion of the enrolled patients may have continued to harbor *H. pylori* infection, even after eradication, and the carcinogenic effect of *H. pylori* may not have been completely eliminated.

A Swedish nationwide population-based cohort study recruited almost 800000 Swedish adults who were undergoing maintenance therapy with PPIs, and the significance incidence ratio (SIR) of gastric cancer was 3.38 (95%CI: 3.23-3.53), which was consistent regardless of gender, age, indications for PPIs (*i.e.*, GERD), concomitant use of anti-inflammatory drugs such as aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) and the subsite of gastric cancer (cardia and non-cardia cancer)[33]. In this study, the authors restricted enrollment to subjects who were exposed to PPI maintenance therapy, defined as a cumulative defined daily dose of at least 180 d during the study period, to reduce the possibility of reverse causality of PPI and gastric cancer. However, this study also failed to establish a causal relationship between gastric cancer and long-term use of PPI, in that the SIR of gastric cancer did not show any duration-dependent pattern. Furthermore, crucial information such as the current *H. pylori* infection status was missing. Clinical studies correlating the long-term use of PPIs with gastric cancer are summarized in Table 1.

Interestingly, clinical outcomes supporting the effect of long-term PPI use on the development of pre-cancerous conditions, such as atrophic gastritis or intestinal metaplasia, are lacking. A previous cohort study showed that 30% (18/59) of patients who were treated with long-term omeprazole and *H. pylori* infection at baseline developed atrophic gastritis, which was significantly higher than non-omeprazole group[34]. Meanwhile, previous randomized controlled trials (RCTs) showed that the proportion of patients who progressed to gastric corpus glandular atrophy and

Table 1 Summary of clinical studies associating gastric cancer with long-term use of proton pump inhibitors

Author, year	Study design, country	Study period	Source of database	No. of case and control	Information of PPI	Adjustment	Main outcomes
Garcia-Rodriguez *et al*[24], 2006	Nested case-control, retrospective, United Kingdom	1994-2001	The general practitioners research database in the United Kingdom	522/10000	Duration, indication	Age, sex, calendar year, smoking, alcohol consumption, body mass index, gastro-esophageal reflux, hiatal hernia, peptic ulcer, and dyspepsia	OR for gastric cardia adenocarcinoma: 1.06 (0.57-2.00); gastric non-cardia adenocarcinoma: 1.75 (1.10-2.79)
Tamim *et al*[25], 2008	Case control, retrospective, Canada	1995-2003	Quebec health insurance plan	1598/12991	Type, dose, exposure time	Number of drug prescriptions, total length of hospitalizations, number of visits to GPs, specialists, and emergency rooms during the year before the diagnosis	Adjusted OR: 1.40 (1.08-1.51); 1st quartile: 1.66 (1.24-2.23); 2nd quartile: 1.37 (1.00-1.88); 3rd quartile: 1.57 (1.17-2.10); 4th quartile: 1.20 (0.85-1.70)
Poulsen *et al*[26], 2009	Population-based cohort, retrospective, Denmark	1990-2003	Danish National Health-care System	109/not reported	Type, year of follow-up, no. of prescription	Age, gender, calendar period, gastroscopy (≥ 1 yr before censoring events), use of NSAIDs and *H. pylori* eradication	IRR for gastric cancer: 1.2 (0.8-2.0) among PPI users with the largest number of prescriptions (15+) or the longest follow-up (5+)
Cheung *et al*[29], 2018	Population-based cohort study, retrospective, Hong Kong	2003-2012	Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority	153/63397	Frequency, duration	Age of receiving *H. pylori* eradication therapy, sex, smoking, alcohol use, comorbidities, concomitant medications	HR for gastric cancer: 2.44 (1.42-4.20); ≥ 1 yr: 5.04 (1.23-20.61); ≥ 2 yr: 6.65 (1.62-27.26); ≥ 3 yr: 8.34 (2.02-34.41). The adjusted absolute risk difference for PPIs *vs* nonPPIs use: 4.29 (1.25-9.54) per 10000 person-yr.
Brusselaers *et al*[33], 2017	Population-based cohort study, retrospective, Sweden	2005-2012	The Swedish Prescribed Drug Registry	2219/794848	Indication, cumulative defined daily dosages, estimated number of days	Age, sex, calendar period, indication of PPI, maintenance use (≥ 180 d) of aspirin or other NSAIDs	SIR: 3.38 (3.23-3.53) in both sexes, all age groups and all indication groups; < 1 yr: 12.82 (12.19-13.47); 1.0-2.9 yr: 2.19 (1.98 to 2.42); 3.0-4.9 yr: 1.10 (0.91-1.31); ≥ 2 yr: 0.61 (0.52-0.72)

PPI: Proton pump inhibitor; OR: Odds ratio; GP: General physician; NSAID: Nonsteroidal anti-inflammatory drug; *H. pylori*: *Helicobacter pylori*; IRR: Incidence rate ratio; HR: Hazard ratio; SIR: Standardized incidence ratio.

intestinal metaplasia was not significantly different between the long-term omeprazole-treated group and the control group[35,36]. A previous study based on histopathologic evaluation of gastric biopsy samples showed that only a small number of patients had worsening of their gastritis score for gastric atrophy and intestinal metaplasia following 12 mo of esomeprazole therapy: 1.4% had atrophy and 0.5% had intestinal metaplasia on the antrum, and 1.2% had atrophy and 0.8% had intestinal metaplasia on the corpus[37]. Recently, the Cochrane Database systematically reviewed four RCTs for the effects of long-term PPI intake on corporal atrophy and intestinal metaplasia. The meta-analysis showed that OR for corporal atrophy was

1.50 (95%CI: 0.59-3.80; P = 0.39), and the OR for intestinal metaplasia was 1.46 (95%CI: 0.43-5.03; P = 0.55), both of which failed to reach statistical significance[38]. Clinical studies associating the long-term use of PPIs with pre-malignant conditions of gastric cancer are summarized in Table 2.

In summary, several studies have shown a significant relationship between long-term PPI use and the risk of gastric cancer. However, the evidence is far from definitive because of limitations of research design and omission of several major confounding variables. Furthermore, conflicting data also exist. For example, although United States is one of the countries with the most frequent and long-term use of PPI, the incidence of gastric cancer is relatively low[39]. Thus, robust evidence including well-designed, large-scale prospective studies are needed to support the potential association between long-term PPI use and gastric cancer

PARADOXICAL ACTION OF PPI IN GASTRIC CANCER CELLS

Effects of PPI on tumor resistance

The unexpected effects of PPIs on solid tumors, including gastric cancer occur by several potential mechanisms (Figure 1).

First, a change of acidity occurs in the tumor microenvironment, for instance in solid tumors, the extracellular pH is acidic and the intracellular pH is neutral-to-alkaline, whereas the pH of the microenvironment in normal tissue usually remains alkaline[40]. This phenomenon leads to decreased intracellular concentrations of cytotoxic drugs that are weakly basic, such as cisplatin, 5-fluorouracil, vinblastine or doxorubicin[12]. PPIs contribute to overcoming drug resistance and enhance chemosensitivity by inhibiting the vacuolar H^+-ATPase (V-H^+-ATPase) of tumor cells, alkalizing the tumor microenvironment and retaining weakly basic cytotoxic drugs within the intracellular targets[11]. An *in vitro* study showed that pretreatment with omeprazole and esomeprazole significantly increased the sensitivity of cytotoxic drugs, such as cisplatin, 5-fluorouracil and vinblastine in various solid cancer cell lines with multi-drug resistance phenotypes[41].

Second, the modulation of cancer stemness plays a role. Cancer stem cells (CSCs) play a key role in the development of chemoresistance as well as cancer metastasis[42]. Several family proteins of ATP binding cassette (ABC) transporters such as P-glycoprotein, multi-drug resistance (MDR) associated protein-1 (MRP-1), lung resistance protein (LRP) and breast cancer resistance protein (BCRP) are highly expressed in CSCs and contribute to MDR by enhancing the activity of drug efflux pumps[43]. PPIs reduce chemoresistance *via* modification of anaerobic glycolysis and ABC transporters in solid cancer cells[44].

Several experimental studies have demonstrated the anti-tumor effects and the ability of PPIs to overcome MDR in gastric cancer. An *in vitro* and *in vivo* study showed that pantoprazole treatment selectively induced apoptotic cell death in gastric cancer cells, while normal gastric epithelial cells were resistant to pantoprazole[45]. Pretreatment of PPIs effectively inhibited the activity of V-H^+-ATPase, which resulted in an increased concentration of cytotoxic drugs in gastric cancer cells[46]. Several *in vitro* studies demonstrated putative downstream effectors following the inhibition of V-H^+-ATPase by PPIs in gastric cancer cells, such as the dephosphorylation of LRP6 and the inhibition of Wnt/β-catenin signaling[47] or PI3K/Akt/mTOR/HIF-1α signaling pathways[48]. A study showed that high-dose esomeprazole inhibited the release of exosomes and exosome-related micro-RNAs such as miR-494-3p, miR-6126 and miR-3934-5p, which are closely associated with tumor invasion, metastasis, adhesion and migration, and in turn, regulated the HIF-1α-FOXO1 axis to induce apoptosis and inhibit cellular migration and invasion in gastric cancer cells[49]. In summary, PPIs modulate the acidic microenvironment, and regulate V-H^+-ATPase and cancer stemness of various cancer cells including gastric cancer, and contribute to the reduction of tumor resistance to chemotherapeutic agents.

PPI modulating SHP-1/STAT3 signaling axis

It is well known that signal transducer and activator of transcription 3 (STAT3) signaling pathway plays a pivotal role in the invasion of gastric cancer[50]. In brief, phosphorylated STAT3 forms a homodimer for nuclear translocation, where it acts as a transcription factor to activate various target genes including cellular migration and invasion in epithelial cells. It also activates surrounding immune cells to regulate various immunologic reactions favoring cancer cell survival, such as the production of inflammatory cytokines and formation of pre-metastatic niches[51]. Various *in vitro* and *in vivo* studies have demonstrated that fully activated STAT3 induced epithelial-mesenchymal transition (EMT) *via* upregulation of relevant target genes such as

Table 2 Summary of clinical studies associating of gastric pre-malignant conditions with long-term use of proton pump inhibitors

Author, year	Study design, country	Source of database	No. of PPI and control group	Information of PPI	Aims	Main outcomes
Kuipers *et al*[34], 1996	Prospective cohort, Netherland/ Sweden	Reflux esophagitis cohort (fundoplication/ omeprazole)	105 (PPI)/ 72 (fundoplication)	Type (omeprazole only), dose (20 and 40mg), duration (5 years)	Corpus gastritis, atrophic gastritis	Atrophic gastritis: 0/31 (fundoplication group) *vs* 18/59 (omeprazole group) with *H. pylori* infection at baseline ($P < 0.001$); 0/41 (fundoplication group) *vs* 2/46 (omeprazole group) without *H. pylori* infection at baseline ($P = 0.62$)
Lundell *et al*[35], 1999	RCT, Sweden	RCT comparing the efficacy of omeprazole and ARS	155 (PPI)/155 (ARS)	Type (omeprazole only), duration (3 years)	Gastric corpus glandular atrophy, intestinal metaplasia of corpus mucosa	No difference in glandular atrophy between *H. pylori*-infected omeprazole and ARS group ($P = 0.57$); No difference in intestinal metaplasia between *H. pylori*-infected omeprazole and ARS group.
Lundell *et al*[36], 2006	RCT, Sweden	RCT comparing the efficacy of omeprazole and ARS	117 (PPI)/98 (surgical arm)	Type (omeprazole only), duration (7 years)	Gastric corpus glandular atrophy	No significant change of gastric atrophy between *H. pylori*-negative omeprazole and ARS group; Two patients developed severe atrophy from none at baseline in *H. pylori*-infected omeprazole group, three patients developed mild atrophy from none at baseline in *H. pylori*-infected ARS group, no statistical difference.
Gental *et al*[37], 2003	Two RCTs, United States	Maintenance trial ($n = 519$), Safety trial ($n = 807$)	Maintenance trial: 519 (PPI)/169 (placebo); Safety trial: 807/PPI	Type (esomeprazole only), duration (6 months: maintenance trial; 12 months: safety trial)	Atrophy (antrum and corpus), intestinal metaplasia (antrum and corpus)	In the maintenance studies, the majority of omeprazole group had no change in the extent of atrophy and intestinal metaplasia. In the safety study, > 98% of omeprazole had either no change or improved atrophy scores in antrum and corpus, and intestinal metaplasia scores remained unchanged or improved compared with those that worsened.

PPI: Proton pump inhibitor; RCT: Randomized controlled trial; ARS: Anti-reflux surgery; *H. pylori*: *Helicobacter pylori*.

vimentin and survivin in gastric cancer cells[52-54]. Furthermore, clinical outcomes also showed that high level of phosphorylated STAT3 were significantly associated with regional lymph node metastasis and poor prognosis in gastric cancer patients[55-57]. STAT3 also plays as a key role in the activation of CSCs. A previous study showed that gastric cancer-derived mesenchymal stem cells (GC-MSCs) secreted interleukin (IL)-6 and activated STAT3 in neutrophils. These GC-MSCs-primed neutrophils

induced transdifferentiation of normal MSCs to cancer associated fibroblasts[58]. Thus, STAT3 may present a primary target for the inhibition of gastric cancer invasion.

Several inhibitors of STAT3 including direct STAT3 inhibitors or inhibitors of upstream kinases, such as janus kinase 2 (JAK2) or Src kinase have been introduced and evaluated in experimental studies[59-61]. However, clinical studies involving gastric cancer patients are lacking, and technical limitations due to large surface of the target area have demonstrated the need for more stable and effective direct STAT3 inhibitors[62]. Src homology 2 (SH2) domain-containing protein tyrosine phosphatase 1 (SHP-1), a non-receptor type protein Tyr phosphatase (PTPase), has attracted attention as an effective inhibitor of STAT3 activity[63]. SHP-1 acts as a protein Tyr PTPase and induces the dephosphorylation of STAT3 in various cell types. It is abundantly expressed and has been mostly evaluated in cells of hematopoietic lineage, such as macrophages, neutrophils, monocytes and mast cells[64]. Pivotal studies demonstrated that the expression of SHP-1 was aberrantly reduced by CpG island hypermethylation in lymphoma and leukemia[65,66]. Recently, the suppressive effect of STAT3 by SHP-1 has been evaluated in solid tumors. Chen *et al*. showed that several multiple kinase inhibitors such as sorafenib, dovitinib and regorafenib effectively induced SHP-1 in hepatocellular carcinoma, and in turn, suppressed STAT3 activity *via* dephosphorylation[67-69]. The function of SHP-1 has been recently evaluated in gastric cancer. Sun *et al*. showed that the expression of SHP-1 was the highest in normal gastric epithelium, followed by intestinal metaplasia and dysplasia and was the lowest in gastric cancer tissues[70], SHP-1 combines with a transmembrane protein with epidermal growth factor and two follistatin motifs 2 (TMEFF2) to inhibit STAT3 phosphorylation in gastric cancer cells and *H. pylori*-infected gastric epithelial cells[71].

We also previously showed that the expression of SHP-1 was aberrantly reduced following CpG island hypermethylation in various gastric cancer cell lines, and enhanced expression of SHP-1 in gastric cancer cells effectively dephosphorylated STAT3, resulting in downregulation of various target genes involved in cellular migration and invasion[72]. An *in vitro* study reported that PPIs exhibited a dose-dependent cytotoxicity and enhanced the sensitivity of cisplatin *via* inhibition of IL-6-stimulated STAT3 activity and its target genes[73]. Recently, we demonstrated that pantoprazole, a well-known PPI, effectively induced SHP-1 and downregulated phosphorylated-STAT3 levels in gastric cancer cells in a dose-dependent manner and modulated EMT markers[74]. Thus, we suggest that PPIs may act as effective STAT3 inhibitors *via* induction of SHP-1 in gastric cancer cells and play a role in the inhibition of progression of gastric cancer.

Application of PPIs in overcoming chemoresistance

Previous studies have demonstrated that the constitutive expression of STAT3 in gastric cancer was closely associated with the MDR of chemotherapeutic agents *via* enhanced expression of various oncogenes and downregulation of apoptotic genes[75]. Enhanced STAT3 activity also induced V-H^+-ATPase in gastric cancer cells, which abrogated the uptake of chemotherapeutic agents and contributed to the development of chemoresistance, as mentioned above[76]. Furthermore, recent studies showed that STAT3 activation reduced the efficacy of trastuzumab, a promising therapeutic antibody targeting HER2, *via* upregulation of MUC1 and MUC4[77], or the positive feedback loop of IL-6/STAT3/Jagged-1/Notch[78]. Thus, effective inhibition of STAT3 activity is considered the mainstay of intervention to overcome chemoresistance and effective management of advanced gastric cancer patients. A previous study demonstrated that pantoprazole effectively inhibited invasion and EMT of adriamycin-resistant gastric cancer cells *via* suppression of the Akt/GSK-β/β-catenin signaling pathway[79]. We recently found that a minimal dose of pantoprazole combined with docetaxel significantly induced SHP-1 expression, downregulated phosphorylation of STAT3, modulated EMT markers, and inhibited cellular migration and invasion in gastric cancer cells. Injection of both pantoprazole and docetaxel into nude mice significantly reduced the tumor volume of xenograft tumors of gastric cancer cells, compared with single administration of each drug[80]. Taken together, we suggest that a combination of PPIs during chemotherapy may play a role in enhancing the sensitivity and efficacy of chemotherapeutic agents including trastuzumab. Experimental studies reporting the effects of PPIs in gastric cancer cells and chemotherapeutic agents are summarized in Table 3. However, the lack of human studies and limited clinical relevance represent challenges that need to be addressed before PPIs are used to increase the effectiveness of chemotherapy for actual gastric cancer and improve patient prognosis. Further pre-clinical and clinical studies that are relevant to this hypothesis are needed.

Table 3 Summary of experimental studies investigating the effects of proton pump inhibitors in gastric cancer cells

Author, year	Study design	Type of PPI	Cell type	Main outcomes	Underlying hypothesis
Yeo *et al*[45], 2004	*In vitro, in vivo*	Pantoprazole	MKN 45, MKN 28, AGS, SNU 601, RGM-1 (normal gastric mucosa cell)	Apoptotic cell death in gastric cancer cells, but not in normal gastric mucosal cells, induced by pantoprazole	Modulation of heat-shock proteins (HSP 70, HSP 27)
Chen *et al*[46], 2009	*In vitro*	Pantoprazole	SGC7901	Inhibition of V-H^+-ATPase expression in a dose-dependent manner; enhancement of efficacy of anti-tumor drug (cisplatin) and increased apoptosis rate	Change of pH gradient (decrease of intracellular pH and reverse of the transmembrane pH gradient)
Shen *et al*[47], 2013	*In vitro*	Pantoprazole	SGC7901	Anti-proliferation, anti-invasive and pro-apoptotic effects, decrease of V-H^+-ATPase expression	Inhibition of LRP6 in Wnt/β-catenin signaling
Chen *et al*[48], 2018	*In vitro, in vivo*	Pantoprazole	SGC7901, SGC7901/MDR	Inhibition of V-H^+-ATPase expression in, SGC7901/MDR cells	Inhibition of P-gp and MRP1, and downregulation of PI3K/Akt/mTOR/HIF-1α signaling pathway
Guan *et al*[49], 2017	*In vitro, in vivo*	Esomeprazole	SGC7901	Enhancement of efficacy of anti-tumor drugs (cisplatin, paclitaxel, 5-FU); Inhibition of transformation of CAF	Regulation of HIF-1α-FOXO1 axis and inhibition of release of exosome and exosome-related microRNAs (tumor invasion, metastasis and TGF-beta pathway)
Huang *et al*[73], 2013	*In vitro*	Pantoprazole	SGC7901, GBC823, AGS	Inhibition of cellular proliferation and increase in the number of apoptotic cells	Inhibition of STAT3
Koh *et al*[74], 2018	*In vitro, in vivo*	Pantoprazole	AGS, MKN-28	Inhibition of cellular invasion, migration and modulation of EMT markers	Induction of SHP-1 and inhibition of JAK2/STAT3
Zhang *et al*[79], 2015	*In vitro*	Pantoprazole	Adriamycin-resistant SGC7901 (SGC7901/ADR)	Inhibition of cellular migration/invasion and modulation of EMT markers in SGC7901/ADR cells	Inhibition of Akt/GSK-β/βcatenin signaling
Joo *et al*[80], 2018	*In vitro, in vivo*	Pantoprazole	AGS	Enhanced cellular migration/invasion and anti-tumor effect of docetaxel by combination with minimal dose pantoprazole	Induction of SHP-1 and inhibition of JAK2/STAT3

PPI: Proton pump inhibitor; V-H^+-ATPase: Vacuolar-H^+-ATPase; LRP6: Low-density lipoprotein receptor related protein 6; MDR: Multidrug resistance; MRP1: Multidrug resistance-associated protein 1; mTOR: Mammalian target of rapamycin; HIF-1α: Hypoxia-inducible factor 1alpha; CAF: Cancer associated fibroblast; FOXO1: Forkhead box protein O1; TGF-beta: Tumor growth factor-beta; EMT: Epithelial-mesenchymal transition; STAT3: Signal transducer and activator of transcription 3; JAK2: Janus kinase 2; ADR: Adriamycin; GSK-β: Glycogen synthetase kinase-3-β.

CONCLUSION

Many physicians have raised concerns that long-term PPI use may be a significant risk factor for GI tract neoplasia, including gastric cancer, and data from recent clinical studies support this hypothesis. However, from a methodological point of view, application of the results from observational clinical studies is limited until solid evidence is available to establish the long-term use of PPI and its association with gastric cancer. However, in patients with pre-malignant lesions such as atrophic gastritis or intestinal metaplasia, it may be necessary to restrict long-term PPI administration, even after *H. pylori* eradication, to prevent gastric cancer. By contrast, theoretical investigations and experimental findings suggest that PPIs may play an

adjunct role of in improving the efficacy of chemotherapy for malignant tumors including stomach cancer. Currently, PPIs might play a "dual role" in gastric carcinogenesis and management of advanced gastric cancer.

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