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# Proton Pump Inhibitors in cancer patients: How useful they are? A review of the most common indications for their use

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ABSTRACT

Proton-Pump Inhibitors (PPIs) are commonly prescribed in the general population and in cancer patients. A supposed role in the prevention of gastric mucosal damage apparently justify their use in patients undergoing cytotoxic chemotherapy, steroids and radiotherapy on the gastro-duodenal region. They are frequently given also to patients admitted to Intensive Care Units, for the prevention of stress-related gastric ulcers. The evidence about these use of gastroprotection is reviewed. In the majority of the cases the prescription of PPIs is not justified. In two circumstances (chemotherapy and stress-related gastric disease) randomized studies have shown a protective action of PPIs although this effect did not translate into the reduction of serious clinical consequences. PPIs are not free of toxic effects that are acknowledged by an expanding literature. Also the interaction with anticancer drugs is a potential source of unwanted consequences.



## 1. Introduction

Gastric mucosal damage is a frequent event in the natural history of cancer. Gastroprotection is widely prescribed due to

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pre-existing or associated conditions. Moreover, cancer patients are frequently exposed to gastric-damaging drugs and potentially riskful clinical conditions. Chemotherapy, steroids, non-steroidal anti-inflammatory agents (NSAID) can have a role in inducing or worsening gastric damage. While the treatment of several diseases, namely peptic ulcer, Helicobacter pylori (HP) gastric damage, Zollinger-Ellison Syndrome and gastroesophageal reflux disease, is established, prevention of gastrointestinal (GI) bleeding, although it gained widespread success, is more debatable. Recognized indications are prolonged NSAID and aspirin (ASA) treatment when associated with other risk factors, such as anticoagulant or steroid concomitant administration and elderly age (Lanza et al., 2009).

Gastroprotection can be achieved using several drugs, although Proton Pump Inhibitors (PPIs) are the most effective agents and have gained a predominant place in drug prescription for both treatment of gastric acid-related disorders and prevention of mucosal damage.

PPIs are irreversible inhibitors of the hydrogen/potassium adenosine triphosphatase (ATPase) system of the gastric parietal cells and achieve a reduction of gastric acid secretion by up to 99%. These drugs have a plasma half-life of 60–90 min, although the covalent binding with ATPase determines a long-lasting inhibition of acid production (24 h). PPIs are the most prescribed drugs in the world. They fall only behind the statins in total spending worldwide, estimated at over US$ 11 billion annually in the USA (Lodato et al., 2016). The prevalence of patients receiving PPIs in the Italian adult population was 22% and up to 55% in people older than 75 in 2014. In the inpatient setting more than 50% of the patients are taking PPIs (Lodato et al., 2016). Expenses for this class of agents are higher than that of anticancer monoclonal antibodies and target agents (Rapporto OSMED, 2014). Gastroprotection is one of the most frequent medical practice at risk of inappropriateness, because it is subject to frequent over-prescription (Heidelbaugh et al., 2012; Forgacs and Loganayagam, 2008; Heidelbaugh et al., 2010). A study conducted in an Ann Arbor, MI Veterans' Administration hospital determined that, out of 946 patients, only 35% were prescribed PPIs for a documented disease, while 36% had no evident indication (Heidelbaugh et al., 2012). In another study conducted on 168,727 adult ambulatory patients approximately 39% received PPIs without any evidence-based indication (Jacobson et al., 2003).

Data available from the Veteran Affairs health care systems suggest that 20–33% of cancer patients currently take acid-reducing agents, with higher frequency in gastrointestinal cancers (35–50%). Of these the large majority are PPIs (Smelick et al., 2013).

Cancer patients are subject to specific risk factors for gastric damage: chemotherapy, radiation therapy (RT) and steroids. Stress gastric ulcers (SGU) are a further clinical condition that frequently involves cancer patients undergoing critical events (sepsis, cancer-related organ failure). In the review we will summarize the available literature and discuss the use of gastroprotective agents in cancer patients, with particular emphasis on PPIs.

## 2. Chemotherapy-induced gastric damage

Chemotherapy (CT) is a well-known inducer of mucosal damage. Historical experience has demonstrated that gastric damage is a frequent occurrence (Sartori et al., 1991). Mucosal gastric damage can present with endoscopical features of diffuse gastritis, erosions or ulcers. Erosions should be distinguished from ulcers: the first are more superficial and do not pass through the muscular layer, leading to lower risk of bleeding and not resulting in perforation. While erosions are frequently described in endoscopic studies of patients undergoing chemotherapy, ulcers are not, because CT-related damage is usually limited to the superficial layers (Sartori et al., 1991). Moreover, while chemotherapy-related erosions are typically found in the antral region, peptic ulcers are preferentially located more proximally, although also duodenal erosion have been described. Several drugs have been related to mucosal damage: cisplatin, anthracyclines, and fluorouracil are the most-commonly described, although case reports have dealt with many other drugs (Gorschlüter et al., 2008). In a comprehensive review on mucosal toxicities of targeted agents (Elting et al., 2013), gastric damage was not considered. Gastrointestinal perforation or hemorrhage was described in case reports for anti-angiogenic agents such as Bevacizumab and Sorafenib and for Erlotinib, an Epidermal Growth Factor Receptor (EGFR) inhibitor. Trastuzumab was shown to cause esophagitis. Gastritis was described in rare cases with the use of Imatinib, Sunitinib and Gefitinib. These toxicities were not included in the ESMO Guidelines on the management of oral and gastrointestinal mucosal injury (Peterson et al., 2015).

While the incidence of mucosal damage is probably high when assessed through serial endoscopies, serious consequences are seldom described and they probably resolve spontaneously when chemotherapy is discontinued. After administration of Cisplatin and Etoposide in 32 patients with lung cancer, mucosal erosions occurred in 16; symptoms were not related with the endoscopic appearance of mucosal damage (Sartori et al., 1991). Loco-regional intra-arterial administration of chemotherapy drugs in the treatment of liver metastases has been associated with more frequent and severe gastric damage (Mavligit et al., 1987). The mechanism of action is not well understood and mucosal damage cannot be completely justified by a direct irritative action. Chemotherapy agents, acting on rapidly proliferating cells, cause cytolysis of the epithelial basal layer, thus inducing impaired renewal of mucosal cells and exposure to the acid gastric content. Other mechanisms, however, have been suggested: Cisplatin blocks the release of acetylcholine in the smooth muscles cells, inducing a pyloric spasm and gastric accumulation of hydrochloric acid and enzymes (pepsin and gastrin) that are able to trigger the mucosal damage. Mucosal hypoperfusion and release of mediators of inflammation are further possible mechanisms (Aggarwal, 1994).

Gastroprotection is intended to prevent the occurrence of mucosal damage and reduce the related symptoms. Five randomized studies of pharmacological gastroprotection have been published (Table 1).

The first was a comparison between placebo and Pirenzepine (a cholinergic antagonist) in 60 patients undergoing various chemotherapy regimens. Pirenzepine induced a reduction of mucosal damage and of the symptoms' frequency (Contu et al., 1989). Similar results were found in another small study (55 patients) comparing placebo with a histamine antagonist (Famotidine) in patients with lung cancer undergoing chemotherapy with cisplatin and etoposide (Mori et al., 1995). A direct comparison of Pirenzepine and famotidine did not find significant differences in a third randomized trial enrolling 38 patients undergoing chemotherapy for lymphoproliferative malignancies (Polloni et al., 1986). Two sequential randomized trials assessed the use of PPIs as prophylactic agents during chemotherapy. The first trial randomized patients undergoing chemotherapy with the CMF regimen (Cyclophosphamide, Methotrexate, and Fluorouracil) for breast cancer and a combination of Fluorouracil and Leucovorin for colorectal cancer (Sartori et al., 1996). Patients underwent an endoscopy before randomization and a further one 7 days after the second cycle. The primary end point of the trial was the difference in terms of number and dimension of mucosal erosions. An evaluation of symptoms (heartburn and pyrosis) was also conducted. In this study a placebo arm was compared with Misoprostol 400 mcg twice daily (a drug interfering with prostaglandin metabolism) and with an association of Misoprostol and Omeprazole at the dose of 20 mg daily. The combination arm resulted in a significant benefit in terms of both endoscopic findings and symptom control (Fig. 1).