Proton Pump Inhibitors in Glioblastoma: From Reflexive Prescribing to Evidence-Based Practice

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Abstract

Glucocorticoids are frequently used in the management of brain tumours to control tumour-associated cerebral oedema and symptoms related to mass effect. Because glucocorticoid exposure may increase the risk of upper gastrointestinal complications in selected patients, proton pump inhibitors (PPIs) are often prescribed prophylactically. Emerging evidence suggests that exposure to PPIs with potent aldehyde dehydrogenase 1A1-activating properties (PA-PPIs) such as omeprazole may be associated with worse progression-free and overall survival in newly diagnosed glioblastoma (GBM). Routine reflexive PPI prophylaxis may therefore not be justified. When acid suppression is clinically indicated, the choice of agent should be individualized, with consideration of H_2-receptor antagonists or antacids where appropriate. These findings support an acid-suppressive stewardship approach in the management of patients with GBM.

Keywords: Glioblastoma, proton pump inhibitors, glucocorticoids, steroids, acid suppression, ALDH1A1.

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Introduction

Neurological symptoms in patients with glioblastoma (GBM) are frequently driven by vasogenic cerebral oedema and intracranial mass effect. Glucocorticoids therefore play an essential role in symptomatic management by reducing oedema and improving associated clinical symptoms.[1] Despite their therapeutic benefit, glucocorticoid therapy can increase the likelihood of upper gastrointestinal (GI) complications, including dyspepsia, gastroesophageal reflux, peptic ulcer disease, GI bleeding, and perforation.[2] To reduce this risk, proton pump inhibitors (PPIs) are often co-prescribed sometimes for extended periods.[2] Emerging preclinical and clinical evidence suggests that certain PPIs, specifically those with potent aldehyde dehydrogenase-1A1 (ALDH1A1) activating properties, known as PA-PPIs, may be associated with inferior survival outcomes in newly diagnosed GBM.[3] This review studies the evidence for and against PPI use in GBM management and argues for risk-stratified, stewardship-based approach to acid suppression in this population.

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Review of Literature:

PPIs are commonly prescribed prophylactically in neuro-oncology practice for patients receiving glucocorticoids, even though routine prophylaxis in the absence of additional GI risk factors is not supported by strong evidence.[3-5] The GI risk attributable to glucocorticoids alone appears low, and when observed, is largely confined to hospitalized or critically ill patients rather than ambulatory patients.[4,5] This risk is amplified by other more established risk factors such as concomitant NSAID, aspirin or anticoagulant use, prior peptic ulcer disease and advanced age.[4,5] Therefore, acid suppression should be stratified by GI bleeding risk rather than prescribed reflexively to all neuro-oncology patients receiving corticosteroids.

When acid suppression is indicated in neuro-oncology patients, PPIs are often the preferred agent, because they provide more potent acid suppression compared to H_2-receptor antagonists and antacids.[3,6,7] PPIs achieve this by irreversibly inhibiting the H^+/K^+-ATPase proton pump in gastric parietal cells while H_2-receptor antagonists only reversibly block parietal-cell H_2-receptors and antacids simply neutralize acid within the gastric lumen.[6,7] Contemporary GERD guidelines continue to position PPIs as preferred therapy for clinically significant acid-mediated disease, including erosive esophagitis, while H_2-receptor antagonists and antacids are generally reserved for selected or adjunctive use.[6,7] Another reason why PPIs may be preferred in GBM patients is because preclinical studies have hypothesized that PPIs may exert antitumour effects by modulating the acidic tumour microenvironment (TME) through inhibition of vacuolar ATPases (ATP6V0A1/2) and disruption of pH gradients that support invasion, survival and drug resistance.[8,9] This reduces invasion in GBM cell lines, increases apoptosis and improves chemotherapy uptake.[8,9] Different PPIs differ in the mechanisms by which they exert their antitumour effect. Omeprazole is reported to inhibit tumour growth and invasion, while rabeprazole inhibits tumour growth and enhances temozolomide (TMZ) sensitivity.[10,11] However, these observations remain

largely experimental; the drug concentrations required to achieve such effects in vitro may exceed clinically achievable maximum plasma concentrations, thus limiting direct translation to patients with GBM.[3,8,9]

In contrast to these proposed antitumour effects, concerns have been raised regarding potential PPI-induced iatrogenesis.[9] One proposed mechanism underlying potential PPI-associated harm is activation ALDH1A1.[8,9] Omeprazole and pantoprazole appear to be more potent activators of ALDH1A1 compared to lansoprazole and rabeprazole.[3] ALDH1A1 activation may promote treatment resistance by reducing oxidative stress and ferroptosis, enhancing DNA repair, and supporting stem-like tumour cell phenotypes through retinoic acid signaling.[9] These mechanisms provide biological plausibility for the adverse survival associations observed with selected PPIs in clinical GBM cohorts, although they do not establish causality by themselves.

The first major clinical signal supporting these mechanistic concerns came from Castro et al., who analysed a US nationwide database of patients with GBM.8 In a multivariable time-varying Cox model adjusted for age, sex, O6-Methylguanine-DNA Methyltransferase (MGMT) promoter methylation status, corticosteroid duration, extent of resection, and initiation of standard therapy, PPI exposure was associated with inferior overall survival.[8] The adverse association was particularly notable among patients with MGMT-methylated tumours.[8] However, the observational study design and broad definition of "any PPI" exposure limited inference regarding whether this risk applied uniformly across all PPIs.

This limitation was addressed by Le Rhun et al., in a pooled individual-patient-data meta-analysis of 2,981 patients with newly diagnosed GBM.[3] They compared PA-PPIs to other antacid drugs in a multivariable analysis adjusted for established prognostic factors.[3] PA-PPI use was associated with worse progression-free survival at landmarks 1, 2, and 3 years, as well as worse overall survival at landmarks 1 and 2 years.3 No comparable association was seen with other antacids.[3] This analysis refined the adverse survival association from general acid suppression to a specific subgroup of PPIs with potent ALDH1A1-activating properties. A subsequent analysis in recurrent GBM disease setting did not confirm an independent association between PA-PPI exposure and survival after multivariable adjustment.[12] However, this likely reflects the therapeutic context and distinct biology of recurrent disease, where

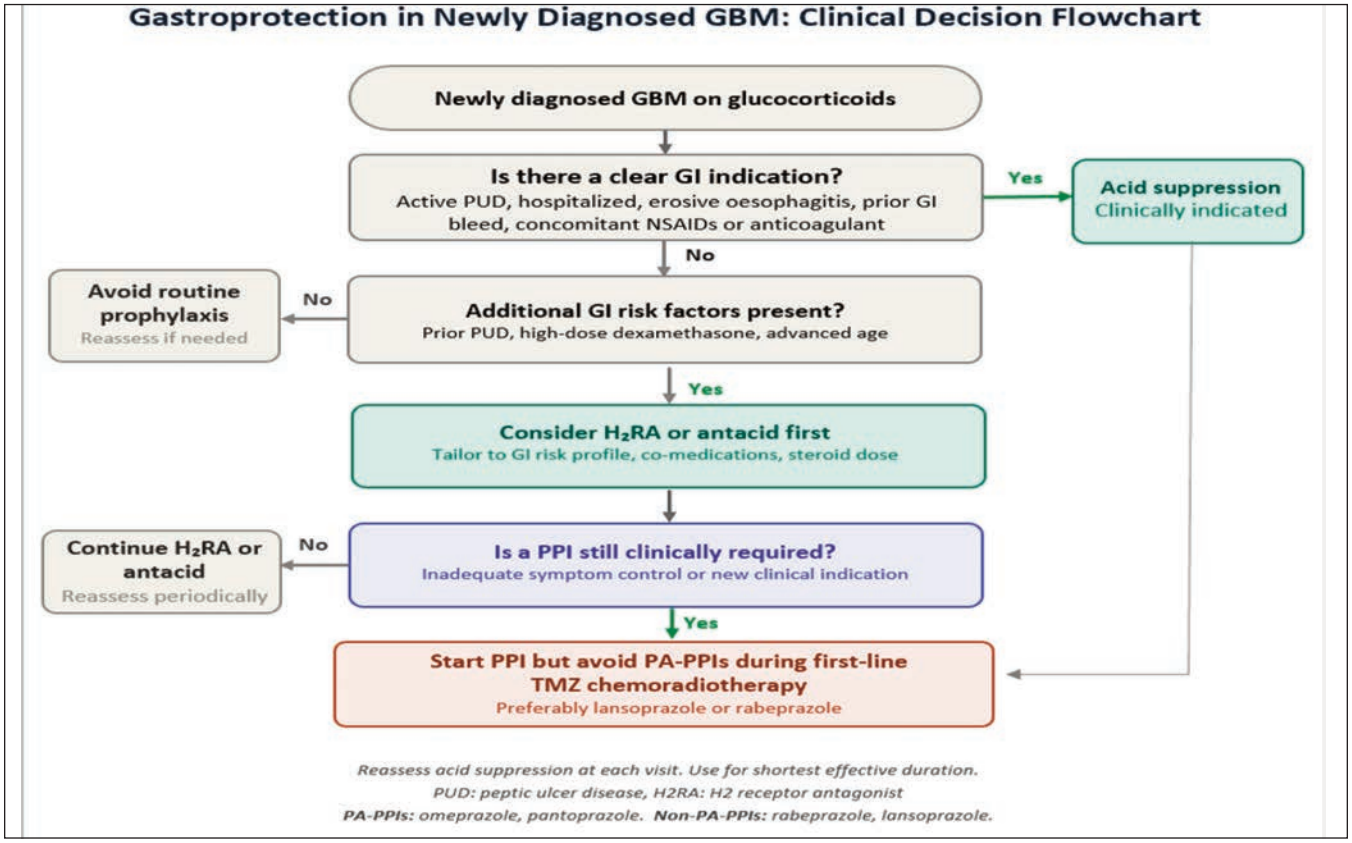

Figure: Summary of clinical decision for acid suppression in newly diagnosed GBM patients.

earlier treatment effects and altered steroid prescribing patterns differ substantially from the newly diagnosed setting.[12] Notably, PA-PPI use in this cohort was strongly linked to corticosteroid exposure, increasing the likelihood of residual confounding in the recurrence setting.[12] These findings should therefore not be interpreted as negating the survival signal observed in newly diagnosed GBM. Rather, they underscore that PA-PPI exposure is context-dependent and that the strongest case for stewardship applies to non-essential PA-PPI use during initial TMZ-based chemoradiotherapy.

Conclusion

The available evidence does not support routine prophylactic PPI use in patients with GBM solely based on glucocorticoid exposure. Although PPIs remain appropriate for clear gastrointestinal indications, their use should be individualized, periodically reassessed, and limited to the shortest effective duration. Caution is especially warranted with PA-PPIs such as omeprazole and pantoprazole during TMZ-based chemoradiotherapy, where both real-world observational data and pooled individual-patient trial data suggest inferior survival outcomes.

When acid suppression is clinically required, H_2-receptor antagonists or antacids may be considered according to the patient's gastrointestinal risk profile, concomitant medications, steroid dose and duration, and overall clinical status. Factors and indications to be considered while selecting acid suppression treatment are summarized in figure 1.

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