Strategies for Chemoprevention in Barrett's Esophagus: The Role of Aspirin, Statins and Acid Suppression

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Abstract

The Barrett's esophagus (BE) is the only known precancerous lesion of esophageal adenocarcinoma (EAC). In the view of poor prognosis after EAC diagnosis, there is considerable interest in the study of disease prevention strategies. The most widely studied types of drugs are non-steroidal anti-inflammatory drugs, statins and proton pump inhibitors. They are shown to be the most promising drugs at present. Cost-benefit analysis shows that aspirin is the most effective strategy for chemoprevention of BE. Combined use of aspirin and statins may have a good cost benefit in BE patients with high risk of EAC progress. Using proton pump inhibitors for chemo prophylaxis for BE patients without gastroesophageal reflux can also significantly reduce the risk of EAC with acceptable cost.

Keywords: Barrett's esophagus; Gastroesophageal reflux disease; Esophageal adenocarcinoma; Chemoprevention; Cost-effectiveness.

Barrett esophagus (BE) is a precancerous lesion of esophageal adenocarcinoma (EAC), which is caused by chronic gastroesophageal reflux disease (GERD). One of the essential diagnostics of BE is the replacement of squamous epithelium by columnar epithelium. BE patients have significant higher risk to develop EAC about 30-40 times (1-4) of BE negative patient. Patients of dysplasia also have higher risk to develop EAC. The annual risk for patients of high dysplasia (HGD) reaches to 7-19% (5-6), while that of low grade dysplasia (LGD) is about 1%. Therefore, chemoprevention for BE progression would help to reduce the cancer deaths.

Most of the current studies focuses on disease chemoprevention strategies. One of the research areas of BE chemoprevention is to avoid the occurrence and development of atypical hyperplasia. The widely used drugs include non-steroidal anti-inflammatory drugs (NSAIDs), statins and proton pump inhibitors.

1. NSAIDs

Owing to the implications of arachidonic acid pathway in the carcinogenesis of BE, cyclooxygenase (COX) inhibitors used as chemotherapeutic agents have received considerable attention.

Epidemiological studies have shown patients using NSAIDs (including aspirin) have significantly reduced the risk of EAC (odds ratio of 0.68). The protection of NSAIDs against EAC would significantly be promoted with the increased duration and frequency of usage (7). Regular use of aspirin or NSAIDs could reduce the risk of BE, especially in patients with GERD (8). Meta-analysis indicated the use of COX inhibitors was associated with a decreased risk of EAC in BE patients. Low dose of aspirin and non-aspirin COX inhibitors could reduce the risk of cancer (9). Studies have shown that aspirin blocks IkB phosphorylation, p65 nuclear translocation, CDX2 promoter activation, and CDX2 expression induced by acid and bile salts in NES-B cells. It may explain the reasons why some GERD patients would develop BE, while some not. It also explains why aspirin can prevent the development of BE (10).

2. Statins

Many observational studies and meta-analyses have shown that long-term use of statins can significantly reduce the incidence of gastrointestinal cancer. Statins have also been studied in chemoprevention of BE.

In BE patients, the use of statins was associated with a decreased incidence of EAC (OR=0.59, 0.50-0.68, 95% confidence interval) (11). Studies have indicated the regular use of statins could significantly reduce the incidence of BE. The effect of combined use of statins and aspirin was more pronounced (12). the use of statins was negatively correlated with the occurrence of EAC. This protective association is the strongest in the late stage of EAC patients. The statin protection was associated with the dose and time of usage, and was not associated with that of non-statin lipid-lowering drugs (13). Among the patients with known BE, the risk of EAC was reduced by 41% with the use of statin (7).

3. Proton pump inhibitors

Proton pump inhibitors (PPIs) are the most widely used drugs for the treatment of

GERD. Many studies have evaluated for their chemoprevention effects on BE.

Prospective and retrospective studies have concluded that PPIs has a protective effect on patients with BE, which can reduce the risk of EAC in BE patients (14-15). Systematic review and meta-analysis showed that the use of PPIs in BE patients reduced the risk of EAC or HGD by 71%, in a dose-response manner (16). Therapy using acid suppression, including drugs and surgery, can reduce the risk of EAC in BE patients, but not completely prevented (17). Recent evidence suggests that PPIs can inhibit the enzyme vacuolar ATP (H+ -VATPase) and interrupt the steadiness of pH, which produce the anti-tumor effect. Omeprazole could inhibit the proliferation and invasion of EAC cells and induce its apoptosis. Reactive oxygen species (ROS) was associated with cell toxicity. These data highly support the potential use of PPIs as a novel anticancer drug for EAC. (18)

4. Cost-effectiveness of chemoprevention

There are several ways to estimate the cost-effectiveness of chemoprevention. The estimation will put the factors of efficacy, cost and safety in consideration. The common calculation is based on the comparison of the cost of additional therapy with that of the standard one and the value is expressed as incremental cost-effective ratio (ICER) that is the cost difference per gain in quality-adjusted life years (QALYs). The estimation on 2003-2004 for the use of aspirin in the chemoprevention of BE to EAC with the assumption of disease progression at 0.5% per year and the efficacy of aspirin at 50%, ICER compared with no prevention therapy was US$12700-18500 per life-year saved (19) and 0.19 more QALYs (20). Patient of BE was identified with high-grade dysplasia has lower ICER at US$3900-$5000 (19). The prevention strategy seems to be improved with the combination of aspirin therapy and endoscopic surveillance, which produced 0.27 more QALYs with ICER at US$49600/QALYs compared with no prevention therapy (20), 0.06 more QALYs with less costs compared with endoscopic surveillance alone (20). Similar result was reported on 2014, aspirin prevention therapy was better performed than endoscopic surveillance alone strategy with 0.167 more QALYs and cost US$6900 less (21). The use of combined treatment of aspirin and statin is expensive, but it could produce cost-effectiveness with ICER compared with aspirin therapy at US$96,000/QALY (21), that was still within the acceptable range of willingness-to-pay threshold of $100,000/QALYs of the year (21). However, when the disease progression of BE to EAC dropped to 0.33% per year, the cost-effectiveness was no long held (21).

For the use of proton pump inhibitor (PPI) as prevention therapy with the assumption of efficacy at 50%, it yielded 0.32 more QALYs with ICER compared with no therapy at US$12,000/QALY (22). Estimation has observed the lowest efficacy allowed for PPI was 19% that would still achieve the cost-effectiveness with ICER compared with no therapy at US$50000/QALY (22). Using PPIs in BE patients without GERD represents a cost-effective strategy to prevent EAC. Future studies require clinical trial data to better assess the effect of PPIs or other chemical prophylaxis on BE patients.

Conclusion

We are increasingly aware of the importance of chemoprevention, but how these drugs act in the carcinogenesis pathway from normal mucosa, to BE and finally to EAC is unknown. A clear understanding of the protective pathway of the drugs is necessary. It would help us to master the optimal timing for intervention, and the development of precise targeted therapeutic agents. It requires carefully designed controlled studies on chemical prevention mechanism. Critical biomarkers predicting the progress of carcinogenesis would be identified. It would help the development on personalized diagnostic method and tailored medicines for chemoprevention.

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Abbreviations:

Barrett esophagus (BE); esophageal adenocarcinoma (EAC); low grade dysplasia (LGD); high dysplasia (HGD); gastro-esophageal reflux disease (GERD); non-steroidal anti-inflammatory drugs (NSAIDs); cyclooxygenase (COX); Proton pump inhibitors (PPIs); Reactive oxygen species (ROS)

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