Standpoint for the management of *Helicobacter pylori* infections in endemic zones for gastric cancer

Henry Montes

CAMIULA, University of Los Andes, Mérida-Venezuela.

Recibido Marzo 25, 2009. Aceptado Marzo 29, 2009

Abstract

In this communication we discuss our stand on *Helicobacter pylori* infection management in endemic regions for gastric carcinoma, considering different clinical situations were elimination of the infection may result in a reduction of gastric cancer prevalence.

KEYWORDS: *Helicobacter pylori, H.pylori* infection, gastric cancer.

PUNTO DE VISTA PARA EL MANEJO DE LAS INFECCIONES POR HELICOBACTER PYLORI *EN ZONAS ENDÉMICAS DE CÁNCER GÁSTRICO.*

Resumen

En esta comunicación se discute nuestro punto de vista sobre el manejo de las infecciones por Helicobacter pylori *en regiones endémicas de carcinoma gástrico, considerando las diferentes situaciones clínicas donde la eliminación de la infección puede traducirse en una disminución de la prevalencia de cáncer gástrico.*

PALABRAS CLAVE: Helicobacter pylori, *infección por* H. pylori, cáncer gástrico.

Infection caused by *Helicobacter pylori* occurs worldwide, but the prevalence varies greatly among countries and among population groups within the same country. The prevalence is associated with socioeconomic conditions: it is around 80 percent in many developing countries conversely to 20 percent in industrialized countries. In Venezuela, a prevalence of *H. pylori* infection between 60-95% has been reported. We have previously described a prevalence of 63% in a group of patients from Mérida-Venezuela (1).

Over the last few years, it has become apparent that the most important single factor responsible for the development of gastric cancer (GC) is *H. pylori* .It has been reported that 800.000 new cases of GC are diagnosed world-wide every year, and from those 600.000 people die in the same time period (2, 3). GC is often resistant to radio and chemotherapy and, indeed, surgery represents the only treatment with a curative potential (4). The risk of *H. pylori*-infected patients to develop GC is in the order of six to twenty times.

H. pylori colonize the gastric epithelium inducing an inflammatory reaction that may persist throughout the patient's life despite a strong local immune reaction. The extension and severity of gastric mucosal inflammation, as well as the clinical outcome of the infection depend on a number of factors including the virulence of the bacterium, host genetic susceptibility, immune response, age at the time of initial infection and environmental factors (5). The complex interplay between these factors may explain why only a minority (<1%) of those infected, ultimately develop GC. The Correa´s multistep model of GC (6), propose a temporal sequence of pathologic changes that led from chronic gastritis to atrophic gastritis, intestinal metaplasia, and dysplasia and the eventual development of GC. The first step was believed to be initiated by a diet rich in salt and nitrates/nitrites as well as due to deficiencies in fresh fruits and vegetables. Nevertheless, after the rediscovery of *H. pylori* by Marshall and Warren (7, 8) and its postulation as having a causal relationship with GC, the microorganism was defined as a definitive carcinogen by the World Health Organization (9).

Gastric adenocarcinoma is generally subdivided into 2 ma in histologic types, based on a classification devised by Lauren in 1965 (10), which recognizes 2 categories: the intestinal (well differentiated) and the diffuse type. The first one is

more common, tends to occur in older patients, and it is more closely linked to environmental and dietary factors. In contrast, the diffuse type of GC is less common, affects young patients, has a worse prognosis, and it has been associated with mutations in the E-cadherin gene. Recent studies indicate that both intestinal and diffuse types of GC are strongly associated with *H. pylori* infection (11).

Although *H. pylori* is now thought to account for 80% or more of GC, it is clear that it is not the only factor in GC pathogenesis. The majority of infected population do not progress to GC, and furthermore, it is very common to find regions with variable prevalence of GC but having the same prevalence of *H. pylori* infection, for example Japan (high) and sub-Saharan Africa (low). To address this point, a study comparing the distribution of virulence-associated genotypes of *H. pylori* in two Colombian populations with contrasting GC risk but with similar *H. pylori* infection prevalence, was designed. They showed that patients proceeding from regions with high risk for GC, showed a significant higher frequencies of cagA positive s1 and m1 genotypes than the population from the low risk area, suggesting that virulence-associated genes from *H. pylori* may be involved (12, 13).

Exposure of gastric epithelial cells to *H. pylori* results in an inflammatory reaction with the generation of reactive oxygen species (ROS) and an increased level of nitric oxide (NO) synthase. NO synthase deamines DNA and causes mutations which may be the initial step in the genetic alterations of gastric epithelial cells (14). The dynamic balance between cell proliferation and apoptosis is essential for maintaining normal mucosal integrity (15).

H. pylori as a carcinogen for cancer of the stomach: two mechanisms have been implicated in the molecular alterations of GC: genetic and epigenetic. The former includes changes in DNA sequence, the latter involves methylation of CpG islands which occurs without DNA sequence changes. The most important difference between genetic and epigenetic alterations is that epigenetic changes are potentially reversible by eliminating the toxic agents or using therapeutic intervention (16). *H. pylori* may induce methylation of promoters containing CpG islands by releasing ROS and NO and activating DNA methyltransferase. Methylation of CpG islands of multiple genes including APC, COX-2, DAP-kinase, E-cadherin, GSTP1, hMLH1, MGMT, p16, p14, RASSF1A, THBS1, and TIMP3, in precancerous gastric lesions have been investigated, and it was shown that aberrant CpG island methylation tends to accumulate along the multistep process of gastric carcinogenesis (16-18). Thus, elimination of *H. pylori* infection has the potential to induce regression of epigenetic alterations and restore normal phenotype. In addition, it has been demonstrated that precancerous lesions such as atrophic mucosal, intestinal metaplasia and non invasive neoplasia, may undergo regression after eradication of *H. pylori* (4).

In countries with moderate- to high-risk GC, and before a stable damage to the mucosa may occur, including the criteria of Maastrich III Consensus report of 2007 (19), we propose that infection caused by *H. pylori* and giving rise to the following conditions:

- Peptic ulcer disease,
- Status post-gastric cancer resection,
- Atrophic gastritis,
- First degree relatives of gastric cancer patients,
- Low grade gastric, mucosa associated lymphoid tissue MALT lymphoma,
- Unexplained iron deficiency anaemia,
- Chronic idiopathic thrombocytopenic purpura,
- Gastric dysplasia,
- Intestinal metaplasia associated with or without lesions indefinite for neoplasia,
- Preview history of cancer,

should be studied as follows: (i) typification of *H. pylori*, a reasonable approach considering that a high virulence of the bacteria could be associated with GC; (ii) upper gastrointestinal endoscopies screening should be performed every 2-3 years in >50 years old patients in high endemic zones, as has been reported recently (2), and (iii) routine cromoendoscopies techniques like indigo carmin should also be included where the use of endoscope with magnification is not available. These would allow us to find early malignant and premalignant lesions that may become a patient eligible for endoscopy, surgery treatment or close follow-up. Finally we have to take in consideration that, eradication of *H. pylori* has the potential to reduce the risk of gastric cancer development.

Correspondence: Henry Montes, MD, Institute of Clinical Immunology, Universidad de Los Andes, Avenida 16 de Septiembre. Edificio Louis Pasteur. Anexo IAHULA, PO BOX 566. Mérida 5101. Venezuela e-mail: montesh@yahoo.com.

Referencias

1. Montes, H., Salmen, S., Dolfo, et al. 2003. Evaluation of a liquid urease test (LUT) for detection of *Helicobacter pylori*. Acta Gastroenterol. Latinoam. 33:73-76.
2. Dan, Y. Y., So, J. B. Y., Yeoh, K. G. 2006. Endoscopic screening for gastric cancer, Clin. Gastroenterol. Hepatol. 4:709-716.
3. Normile, D. 2008. The promise and pitfalls of clinical trials overseas. Science 322: 214-216.
4. Nardone, G., Rocco, G., Malfertheiner, P. 2004. *Helicobacter pylori* and molecular events in precancerous gastric lesions. Aliment. Pharmacol. Ther. 20:261-270.
5. Graham, D. Y., Go, M. F. 1993. *Helicobacter pylori:* current status, Gastroenterology 105:784-791.
6. Correa, P., Haenszel, W., Cuello, C., et al, 1975. A model for gastric cancer epidemiology. Lancet 2:58-60.
7. Marshall, B. J. 1983. Unidentified curved bacillus on gastric epithelium in active chronic gastritis. Lancet 1:1273-1275.
8. Marshall, B. J., Warren, J. R. 1984. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1:1311-1315.
9. Konturek, J. W. 2003. Discovery by Jaworski of *Helicobacter pylori* and its pathogenetic role in peptic ulcer, gastritis and gastric cancer. J. Physiol. Pharmacol. Suppl. 3:23-41.
10. Lauren, P. 1965. The two histologic main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. An attempt at a histoclinical classification. Acta Pathol. Microbiol. Scand. 64:31-49.
11. Uemura, N. O. S., Yamamoto, S., Matsumura, N., et al. 2001. *Helicobacter pylori* infection and the development of gastric cancer. N. Engl. J. Med. 345:784-789.
12. Agha, A., Graham, D. Y. 2005. Evidence-based examination of the African enigma in relation to *Helicobacter pylori* infection. Scand. J. Gastroenterol. 40:523-529.
13. Bravo, L. E., van Doom, L. J., Realpe, J. L., Correa, P. 2002. Virulence-associated genotypes of *Helicobacter pylori*: do they explain the African enigma? Am J Gastroenterol. 97:2839-2842.
14. Papa, A., Danese, S., Sgambato, A., et al. 2002. Role of *Helicobacter pylori* CagA+ infection in determining oxidative DNA damage in gastric mucosa. Scand. J. Gastroenterol. 37:409-413.
15. Kuipers, E. J., Meuwissen, S. G. 1996. *Helicobacter pylori* and gastric carcinogenesis. Scand. J. Gastroenterol. 218:103-105.
16. Peek, R. M. J., Schneider, B. G., Correa, P. 2006. Coming unglued. Clin. Cancer Res. 12:2951-2954.
17. Augusto, A. C., Miguel, F., Mendonça, S., et al. 2007. Oxidative stress expression status associated to *Helicobacter pylori* virulence in gastric diseases. Clin. Biochem. 40:615-622.
18. Kanai, Y., Hirohashi, S. 2007. Alterations of DNA methylation associated with abnormalities of DNA methyltransferases in human cancers during transition from a precancerous to a malignant state. Carcinogenesis 28:2434-2442.
19. Malfertheir, P., Megraud F., O'Morain C., et al. 2007. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. Gut 56:772-781.