Clinical Update

The dyspepsia dilemma

Talley NJ, Vakil N, Ballard ED II, Fennerty MB. Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med* 1999;341(15):1106-11.

Background

Dyspepsia is one of the most frequent presenting complaints in primary care practice. More than 50% of affected patients do not have an ulcer, but as many as 30% may have *Helicobacter pylori* infection, indisputably the main cause of peptic ulcer. Various expert groups have issued recommendations, largely on the basis of consensus (i.e., no direct evidence), for and against therapy to eradicate *H. pylori*.

Question

Should patients with dyspepsia and positive test results for *H. pylori* be treated for eradication of the bacterium?

Design

A randomized controlled trial involving 170 patients with nonulcer dyspepsia (confirmed by endoscopy) and *H. pylori* infection were randomly assigned to receive triple therapy for eradication of the bacterium (omeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, twice daily for 14 days); 167 control subjects with the same condition were given identical-appearing placebos. Successful treatment was defined as the absence of symptoms or only mild pain or discomfort. The study was undertaken at multiple centres in the United States.

Results

At 12 months 46% of the subjects in the treatment group and 50% of those in the placebo group reported either no discomfort or no more than mild pain or discomfort in the upper abdomen during the 7 days preceding the assessment. The mean rate of antacid use was similar in both groups at 12 months. Urea breath test results 4–6 weeks after termination of active treatment indicated that 90% of the patients in the treatment group had negative results for *H. pylori*, as compared with 2% of those in the placebo group. In a subset of patients with chronic gastritis diagnosed during their entry gastroscopy, 86% of those in the treatment group no longer had the problem, as compared with 8% of those receiving placebos. When endoscopy was performed after 12 months, duodenal ulcer was found in 2% of the treated patients and 4% of the control subjects ($p = 0.22$).

Commentary

This was a carefully conducted, randomized, double-blind, placebo-controlled clinical trial. The primary outcome measure (symptom relief) is relevant. The authors also documented the presence of peptic ulcer at the final visit, did pill counts of antacid use and collected a variety of other measures of patient well-being that are not reported here. The study was multicentred; although the precise number of centres was not stated, each centre enrolled 6 patients on average. It is unclear whether patients in this study were similar to those seen in a primary care practice.

Implications for practice

Patients with moderate pain or discomfort in the upper abdomen (dyspepsia) who do not present with warning signs of more serious disease (age less than 50 or signs of blood loss) may have *H. pylori* infection. This study shows that the eradication of *H. pylori* does not convey a health benefit. The implication is that patients presenting with moderate upper abdominal discomfort but without warning signs do not require testing for *H. pylori* infection and should be managed with conventional therapy. A recent meta-analysis supports this recommendation.[1] — *John Hoey*, CMAJ

Reference

1. Danesh J, Pounder RE. Eradication of *Helicobacter pylori* and non-ulcer dyspepsia. *Lancet* 2000;355:766-7.

Breast cancer and distant metastatic disease

Braun S, Pantel K, Müller P, Janni W, Hepp F, Kentenich CRM et al. Cytokeratin-positive cells in the bone marrow and survival of patients with stage I, II, or III breast cancer. *N Engl J Med* 2000;342(8):525-33.

Background

Many women with breast cancer that appears localized to the breast or to the breast and regional lymph nodes are believed to have undetectable distant metastases at the time of initial staging. Because of this, current recommendations are that systemic chemotherapy be given to all women with regional node involvement and to those with no node involvement but a primary lesion greater than 1 or 2 cm in diameter. However, the improvement in outcome with chemotherapy is slight. In women

with a primary tumour of 1 cm or less, systemic therapy reduces the rate of distant metastases from 10% to 7%. Although this is a risk reduction of 40%, it means, in effect, that an average of only 3 women on average in every 100 actually benefit from the therapy.[1] Thus, many women may needlessly undergo chemotherapy. However, if distant metastatic disease could be detected at the time of initial cancer diagnosis, the precision of prognostic stratification might be improved. A new technique to detect bone marrow micrometastatic lesions is now available.

Question

What proportion of women presenting with stage I, II or III breast cancer have distant metastatic disease?

Design

Bone marrow aspirates from the upper iliac crests were obtained from 743 consecutive patients admitted to a breast clinic in Germany; 552 had been newly diagnosed with stage I, II or III breast cancer and 191 patients with nonmalignant disease (mainly of the breast). The patients were followed for several years, thus providing some information on the test's usefulness in categorizing women into meaningful risk groups.

Results

Using an immunocytochemical technique to detect an antigen on cytokeratin peptides (a specific marker of epithelial cancer cells in bone marrow), 36% of the women with breast cancer tested positive, compared with only 1% of women without breast cancer. During a median follow-up period of 38 months, women with marrow-detectable cytokeratins were much more likely to die of cancer-related causes than women without the markers (relative risk 4.17; 95% confidence interval 2.51–6.94; $p < 0.001$). There were 301 women with no detectable lymph-node metastastes. Cytokeratin markers were found in the bone marrow of 23% of women with tumours smaller than 0.5 cm and 35% of those with tumours 0.5 to 1.0 cm. Of the 100 patients with node-negative tumours and evidence of micrometastases, 14 died of cancer-related causes over the follow-up period, compared with only 2 of the 201 women without micrometastases.

Commentary

This is a carefully conducted study of a large cohort of women. The testing for cytokeratins was done independently from the clinical staging. However, follow-up was relatively short, especially for a disease such as breast cancer.

Clinical implications

In a related editorial,[1] Barbara Smith comments that it is now important to proceed with trials of therapy because the follow-up is relatively short for breast cancer. Nonetheless, the survival curves extending to 48 months show a continuous divergence of survival and disease-free survival between groups with and without micrometastases. Smith feels that it is premature to recommend cytokeratin tests to patients with disease limited to the breast who wish to avoid chemotherapy. — *John Hoey*, CMAJ

Reference

1. Smith BL. Approaches to breast-cancer screening. *N Engl J Med* 2000;342(8):580-1.

Amok enzymes damage tissues during heart attack

A team of University of Alberta researchers has discovered a cause of the tissue damage that occurs during heart attacks and, in the process, added a wrinkle to current thought on the role of bacterial infections in heart disease (*Circulation* 2000;101:1833).

Led by Dr. Richard Schulz, an Alberta Heritage researcher, the team has come up with striking evidence that the enzyme matrix metalloproteinase-2 (MMP) is responsible for some injuries to heart tissues in the seconds following the onset of a heart attack. What's more, the authors say a novel side effect of tetracycline-class antibiotics that inhibits the action of MMPs must be taken into consideration by researchers probing the involvement of bacteria in heart attacks.

Schulz likens the role of MMPs to a bulldozer parked in your garage — the garage being one of your cardiac muscle cells. In an experimental model of heart attack in rat hearts, the researchers discovered that MMPs, commonly associated with wound healing, were responsible for injury. Beginning mere seconds after the onset of a heart attack, MMPs run amok. It is, Schulz says, as if someone was driving the bulldozer around inside the garage, causing tremendous damage.

They discovered that tetracycline-class antibiotics block the action of MMPs during heart attacks and reduce damage. The drugs can be modified to inhibit only MMPs, so that their use for nonbacterial conditions such as this would not add to the problem of bacterial resistance to antibiotic drugs.

"The question now is for those people who are susceptible to heart attacks — for example, patients with a previous history or angina — whether this class of inhibitors could be used as a prophylactic measure." Other research has drawn links between bacteria and heart attacks. Schulz's team hasn't disproved any connection, but he says its findings cannot be ignored.

"The bacteria angle needs a lot more research," he says. "It really captures the imagination of researchers. People are saying 'Maybe we will find a bacteria that causes some forms of heart attack,' and they may be right. But we are just saying there are novel protective elements of tetracyclines that you have to consider." — *Richard Cairney*, Devon, Alta.