This opinion is based on our recent analysis of 879 consecutive patients referred with suspected MUO. These patients were evaluated to assess the contribution of studies specific to the identification of occult primary tumors (3). We found that the diagnostic evaluation could be focused by emphasizing careful pathologic analysis and radiographs designed to evaluate women for breast or ovarian primary tumors. With this strategy, not only were primary tumors identified in 20% of the patients with suspected MUO, but what is more important, primary tumors that were highly treatable or had good survival based on their favorable natural history were frequently identified. While we did not specifically address the time consumed in the evaluation of these patients, clearly the most time-consuming process is the uncritical use of exhaustive or poorly thought-out diagnostic testing.

Rather than concentrating intensive investigations into an arbitrary time limit, our studies suggest that patients with MUO can be identified once the following studies have been completed: 1) history and complete physical examination (including a pelvic examination in women and testicular and prostate palpation in men); 2) stool occult blood test, serum multichannel blood analysis, complete blood cell count, and prostate-specific antigen (in men); and 3) chest x ray, computerized tomography of the abdomen and pelvis, and bilateral mammography (in women).

Abnormalities identified in the screening evaluation outlined above are evaluated with diagnostic tests appropriate to that finding. Furthermore, with the emerging availability of increasingly sophisticated cytogenetic and molecular diagnostic studies, planning an efficient evaluation requires a biopsy of a metastatic lesion early in the diagnostic process and close collaboration between clinician and pathologist.

Adopting a focused evaluation, such as that described above, will minimize the time required to complete the evaluation of patients with suspected MUO. Although we agree with the general philosophy that efficient evaluation and expeditious therapeutic decision making with respect to these patients are essential, we believe the specific diagnostic studies applied to the evaluation are the variables appropriate to the definition of patients with MUO.

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Note

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Paclitaxel Premedication Regimens

Hypersensitivity reactions (HSRs), including hypotension, dyspnea, angioedema, and urticaria, have been a problem associated with the administration of paclitaxel (Taxol; Bristol-Myers Squibb, Wallingford, CT). Phase I trials were delayed because of HSRs, which were reported in up to 40% of the patients (1,2). Consequently, it was recommended that the infusion time for paclitaxel be prolonged to 24 hours and that a three-drug premedication regimen be administered to decrease or prevent the incidence of HSRs (1,2).

The exact cause of paclitaxel-associated HSRs is unclear, but the release of mast cell mediators (such as histamine), complement activation, and increased vascular permeability may be involved, perhaps in a manner similar to that of anaphylactoid reactions secondary to exposure to iodinated radiocontrast media (RCM) (1,2). For this reason, a premedication regimen consisting of dexamethasone, diphenhydramine, and cimetidine or ranitidine was recommended, based on similar regimens that are useful in preventing reactions to RCM (1,3-6).

Major and minor HSRs now occur in less than 2% and 40% of patients, respectively (7). Subsequent studies (7-10) have shown that shorter infusion times of 3 hours and 1 hour, given on an outpatient basis, do not result in an increased incidence of HSRs. The likelihood of HSRs occurring appears to be greatest during the first or second cycle of paclitaxel administration, particularly during the first 10 minutes of infusion (1). HSRs occurring after these cycles have been rare (1).

The actual benefit of a histamine2 antagonist, such as cimetidine or ranitidine, in the premedication regimen is questionable and may even increase HSRs to RCM when compared with prednisone plus diphenhydramine (3). To the best of our knowledge, the best premedication regimen studied for RCM employs prednisone, diphenhydramine, and ephedrine (if there is no contraindication to a beta-receptor agonist). It appears that this regimen has not been studied in the context of paclitaxel administration, despite its increased efficacy in preventing RCM-induced HSRs.

High dose dexamethasone (20 mg orally/intravenously) 12 and 6 hours prior to paclitaxel administration has been proposed to be a well-tolerated regimen to prevent HSRs. In our experience, this type of dexamethasone dosing can result in adverse effects, including steroid withdrawal symptoms, hyperglycemia, confusion and memory loss, insomnia, gastric discomfort, myopathy, and depression. The incidence of these adverse effects may increase in time, since many patients require multiple cycles of paclitaxel. Uziely et al. (11) describe comparable reactions to dexamethasone, and they have been gradually reducing the dose of dexamethasone for subsequent cycles of...
Corticosteroids have nonspecific anti-inflammatory activity. They depress the formation, release, and activity of endogenous chemical mediators of inflammation (e.g., kinins, histamine, and prostaglandins); they also inhibit cell migration to areas of injury, decrease capillary dilatation, and reduce blood vessel permeability in areas of injury (12). Corticosteroids are generally administered several hours prior to procedures where there is a high risk of HSRs because the onset of anti-inflammatory actions can be delayed (12), thus, the recommendations for doses to be given 12 and 6 hours prior to paclitaxel treatment. Such a schedule is somewhat inconvenient for patients, given that they may have to awaken during the early morning hours to ingest a dexamethasone dose. In addition, the dose and schedule of dexamethasone administration may be somewhat arbitrary for several reasons: 1) there are successful reports of intravenous corticosteroid administration immediately prior to the administration of RCM in emergency situations (13); 2) high doses of dexamethasone given 24 hours prior to paclitaxel do not universally prevent HSRs in patients who have previously experienced HSRs from paclitaxel (14); and 3) the onset of anti-inflammatory reactions from corticosteroids is reported to be 4-6 hours (12), and the biological half-life of dexamethasone is 36-72 hours (12). A single, intensive dose of dexamethasone may, therefore, be sufficient if given early enough prior to paclitaxel treatment. The dose of prednisone used for RCM prophylaxis was 150 mg given in three divided doses (3-6). An equivalent anti-inflammatory dose of dexamethasone is approximately 22.5 mg (12); therefore, the currently recommended dose of dexamethasone (20 mg orally 12 and 6 hours before paclitaxel) may be larger than required to prevent HSRs.

We would like to report on eight patients who have received more than 26 cycles of paclitaxel via 3-hour infusions and did not receive conventionally recommended paclitaxel premedication prior to the first or subsequent cycles. None of the patients experienced any HSRs. In five patients (21 cycles), a histamine2 antagonist was not administered. All cycles except two were preceded by diphenhydramine treatment. The diagnoses included breast cancer (two patients [Nos. 1 and 3]) and ovarian cancer. The dexamethasone doses employed are shown in Table 1.

Preliminary findings in the literature suggest that it is safe to reduce the dose of dexamethasone following cycle 1 of paclitaxel treatment. The purpose of our correspondence is to document findings similar to those of Uziely et al. (11) and to report that reduced doses of dexamethasone could be employed from the start of paclitaxel therapy. Further study needs to be conducted to elaborate the mechanism of paclitaxel-induced HSRs and risk factors that identify those patients at greatest risk of HSRs. Also, randomized, controlled clinical trials need to be performed to address the dose and schedule of dexamethasone administration prior to paclitaxel treatment and to address the benefit of histamine2 antagonists and ephedrine in preventing HSRs related to paclitaxel.

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Saskatoon Cancer Centre

Ovarian cancer high-dose versus low-dose

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Table 1. Dexamethasone dose

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tumor</th>
<th>Cycle No.</th>
<th>Dexamethasone dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breast</td>
<td>1</td>
<td>10 mg iv immediately prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-6</td>
<td>10 mg po 12 and 6 h prior</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg iv immediately prior</td>
</tr>
<tr>
<td>2</td>
<td>Ovarian</td>
<td>1-3</td>
<td>4 mg po 12 and 6 h prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg iv immediately prior</td>
</tr>
<tr>
<td>3</td>
<td>Breast</td>
<td>1</td>
<td>10 mg po hs prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg po immediately prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-3</td>
<td>10 mg po hs prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg iv immediately prior</td>
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<tr>
<td></td>
<td></td>
<td>4</td>
<td>10 mg iv immediately prior</td>
</tr>
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<td></td>
<td></td>
<td>5-10</td>
<td>4 mg po hs prior only</td>
</tr>
<tr>
<td>4</td>
<td>Ovarian</td>
<td>6</td>
<td>8 mg po 12 and 6 h prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg iv immediately prior</td>
</tr>
<tr>
<td>5</td>
<td>Ovarian</td>
<td>3</td>
<td>4 mg po hs prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg po 6 h prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg iv immediately prior</td>
</tr>
<tr>
<td>6</td>
<td>Ovarian</td>
<td>3-7</td>
<td>10 mg po 12 and 6 h prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg iv immediately prior</td>
</tr>
<tr>
<td>7</td>
<td>Ovarian</td>
<td>2-6</td>
<td>4 mg po hs prior, then every 6 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg iv immediately prior</td>
</tr>
<tr>
<td>8</td>
<td>Ovarian</td>
<td>1</td>
<td>4 mg po hs prior, 6 h prior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg iv immediately prior</td>
</tr>
</tbody>
</table>

*po = orally; iv = intravenously; and hs = at bedtime.

Note
Correspondence to: Darryl Boehm, B.S.P., Department of Pharmacy, Pasquon Hospital, 410 Dewdney Ave., Regina, Saskatchewan, S4T 1A5, Canada.

Re: Helicobacter pylori and Atrophic Gastritis: Importance of the cagA Status

We read with great interest and fully concur with the findings reported by Kuipers et al. (1) in a recent issue of the Journal; most importantly, they concluded that infection by Helicobacter pylori (H. pylori) of the cagA (cytotoxin-associated gene A) strain is of importance in defining gastric cancer risk.

Three years ago, we started a research network on gastric cancer and precursor lesions, which we named MHEPHISTO (Metaplasia Helicobacter pylori Histology). Within this program, we follow prospectively patients with gastric cancer who are under our care at our hospitals in Turin, Italy.

The patients were given a 13C-urea breath test for the detection of H. pylori infection according to the European standard (2) and blood samples were taken and analyzed for antibodies against H. pylori. Total immunoglobulins against H. pylori were tested by use of a commercial enzyme-linked immunosorbent assay, while anti-cagA antibodies were identified by use of an enzyme-linked immunosorbent assay designed to detect serum immunoglobulins directed against the cagA protein (3,4). The antigen used in the test was from A. Covacci (IRIS Biocine, Siena, Italy).

Of the 51 patients operated on for gastric cancer and in whom we tested for antibodies to the cagA protein, 49 (96%) were found to be positive. Hence, we defined them as being infected by the cagA-positive strain of the bacterium. We estimate that the general population of Turin carries an 18% positivity for anti-cagA antibodies as determined by testing 555 consecutive individuals admitted to the Emergency Care Unit of our hospital during August 16-31, 1994 (5). The risk of dying from gastric cancer in Turin is 2.3% (cumulative risk based on individuals aged 0-74 years) (6). Thus, it is probable that one of every eight anti-cagA-positive individuals in our city will die of gastric cancer before reaching 74 years of age.

We are unaware if other populations are similarly at risk, but Dr. Kuipers' report seems to signal that this may be so in the Dutch population as well. Considering the findings of Kuipers et al. (1) and our own, we believe that in defining gastric cancer risk, we should not overzealously suspect H. pylori unless it has been shown to have the cagA gene. Instead, we recommend that people aged 45 years and older in Turin be tested for anti-cagA antibodies. Those individuals testing positive should then be offered upper gastrointestinal tract endoscopy with multiple biopsies to identify diffuse atrophic gastritis and intestinal metaplasia, two conditions placing these patients at an increased risk of cancer.

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MAURIZIO DEGIULI

References

Note
Correspondence to: Antonio Ponzetto, M.D., Division of Gastroenterology, Exp1, Dept. GI, Ospedale S. Giovanni Battista, 10126, Turin, Italy.

Response
We appreciate the reaction of Ponzetto et al. to our report concerning the presence of cagA (cytotoxin-associated gene A) serum antibodies and the risk of the development of atrophic gastritis. The observations communicated in their letter are potentially very valuable and further support the hypothesis that infection with a cagA-positive H. pylori strain imposes a greater risk for the development of atrophic gastritis and gastric cancer than does infection with a cagA-negative strain. This association has now been reported to exist in three different populations around the world: inhabitants of Italy and The Netherlands and Japanese-American men from