Failure of Pretreatment With Intravenous Folic Acid to Alter the Cumulative Hematologic Toxicity of Lometrexol

Treatment with lometrexol, an inhibitor of de novo purine synthesis, is complicated by severe stomatitis and cumulative pancytopenia (1-4). Since maximal antitumor effects in mice required normal rather than depleted folate stores (5), clinical trials later included folate repletion (6-8). Daily oral folic acid and lometrexol (up to 5 mg/m²) given twice weekly were well tolerated (6,7). In a trial stopped early, 2 mg but not 1 mg folic acid with lometrexol (5 mg/m² weekly for 3 weeks) minimized stomatitis and thrombocytopenia (8). Other investigators (8-11); Natty S, Pagano O, Cavalli F; manuscript submitted for publication) used folates to escalate lometrexol dose. In the study by Sessa et al., oral leucovorin (15 mg, four times daily) was administered on days 7-9, and the lometrexol dose was increased to 60 mg/m² every 4 weeks with no grade 3 or 4 toxic effects (National Cancer Institute Common Toxicity Criteria) in six patients. In other studies (8,9), 5 mg folic acid was given daily from 7 days before and 7 days after lometrexol administration, which allowed 170 mg/m² lometrexol to be administered every 3 weeks. In another study 5 mg folic acid was continuously administered daily; as a result, lometrexol could be administered at 8 mg/m² per week for 12 weeks. Thus, oral leucovorin or folic acid improves tolerance to lometrexol. Responses noted in refractory ovarian cancer and other cancers were not related to the lometrexol dose.

In this phase I study, 5 mg folic acid was given intravenously 1 hour before lometrexol every 3 weeks. Dose-limiting toxicity was defined as grade 3 nonhematologic or any grade 4 toxicity, and escalation of the lometrexol dose ceased if two or more patients experienced a dose-limiting toxicity. A sensitive, new high-performance liquid chromatography assay measured pharmacokinetics on the day of therapy; plasma and whole blood levels of lometrexol were ascertainment weekly (Synold TW, Xi B, Newman EM, Muggia FM, Doroshow JH; manuscript submitted for publication).

With verification of dose-limiting toxic effects on cycles 2 and 3 of the first level (30 mg/m²), the lometrexol dose was decreased to 15 mg/m². The study was also amended to treat patients with 25 mg/m² folic acid, which was given intravenously 3 hours before lometrexol (Table 1) based on the timing of 5-methyltetrahydrofolate peak levels (12). Previously, upon entry into the study, patients received 20 mg/m² lometrexol, and new cohorts at 15, 20, and 30 mg/m² received such pretreatment. Noted were grade 4 neutropenia in patients on cycle 3 with 20 mg/m² lometrexol, grade 3 mucositis in patients on cycle 2 with 30 mg/m², and grade 4 thrombocytopenia in patients on cycle 2 with 30 mg/m². These toxic effects prompted study closure after accrual of 12 men and 12 women.

### Notes

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### References


### Table 1. Dose levels and toxic effects in relation to drug courses

<table>
<thead>
<tr>
<th>Dose of lometrexol, mg/m²*</th>
<th>Folic acid pretreatment</th>
<th>No. of patients</th>
<th>Grade 3 or 4 toxic effects (course No.)</th>
<th>No. of patients transfused (course No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>5 mg</td>
<td>3</td>
<td>Neutropenia (2 and 3) and anemia (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>25 mg/m²</td>
<td>3</td>
<td>Fatigue (3)</td>
<td>2 (1 and 3)</td>
</tr>
<tr>
<td>20</td>
<td>5 mg</td>
<td>3</td>
<td>Thrombocytopenia (3), anemia (2 and 3), and stomatitis (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td></td>
<td>25 mg/m²</td>
<td>3</td>
<td>Stomatitis (2) and neutropenia (3)</td>
<td>—</td>
</tr>
<tr>
<td>25</td>
<td>25 mg/m²</td>
<td>3</td>
<td>No toxic effects greater than grade 2</td>
<td>—</td>
</tr>
<tr>
<td>30</td>
<td>5 mg</td>
<td>3</td>
<td>Anemia (2), fatigue (2), and stomatitis (2)</td>
<td>1 (2 and 4)</td>
</tr>
<tr>
<td></td>
<td>25 mg/m²</td>
<td>6†</td>
<td>Mucositis (2) and fatigue (3)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Given every 3 weeks.
†Only four patients received a second course; others had tumor progression.
We conclude that pretreatment with intravenous folic acid does not substantially alter the cumulative toxic effects of lometrexol. This conclusion is reinforced by the finding that, at all dose levels, lometrexol uptake into red blood cells rose steadily and paralleled falls in hematocrit levels (13). If erythrocyte levels of lometrexol reflect tissue levels, the levels of lometrexol reflect tissue levels, lometrexol uptake into red blood cells in various settings may help determine why daily oral but not one dose of intravenous folic acid avoids cumulative toxicity. Red blood cell uptake and release from this reservoir have also been implicated in the neurotoxicity of oxaliplatin (14). Future studies with lometrexol and new antifolates should include assessment of drug accumulation in erythrocytes.

No antitumor effects were recorded among 11 patients with colorectal cancer, six with respiratory cancer, four with gynecologic cancer or breast cancer, and three with miscellaneous cancers. One exception was a minimal lowering of CA-125 in a patient with ovarian cancer, who received four doses of lometrexol at 20 mg/m².

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References


Notes

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Re: Second Cancers After Adjuvant Tamoxifen Therapy for Breast Cancer

Curtis et al. state "...we found little evidence that tamoxifen treatment increases the incidence of colorectal or stomach cancer significantly, as reported by Rutqvist et al." (1). In fact, the data of Curtis et al. offer little evidence to controvert the findings of Rutqvist and colleagues from the Stockholm Breast Cancer Study Group (2).

The data from the Surveillance, Epidemiology, and End Results (SEER) Program (1) that Curtis et al. present may be biased toward the null value by the failure to consider induction time. This failure is equivalent to assuming that the latent period for tamoxifen-induced gastrointestinal cancers is zero. This assumption results in the dilution of data on truly exposed patients who have had sufficient time to develop the disease under study with data on patients who would be more correctly categorized as unexposed (3). Such dilution is especially important given the short follow-up of the SEER study—the mean duration of follow-up for the tamoxifen-treated group was only 2.8 years (14 358 patients; 39 736 person-years at risk). In contrast, the median follow-up for the patients reported by the Stockholm Breast Cancer Study Group was 8-9 years.

In spite of this bias in follow-up time, the 95% confidence intervals for the odds ratios for stomach and colorectal cancers reported by Curtis et al. overlap those of the Stockholm Breast Cancer Study Group and remain consistent with a 30%-49% increase in risk of colorectal cancer and as much as a 103% increase in risk of stomach cancer. Clearly, further data obtained from patients exposed to tamoxifen for longer periods will be required before we can dismiss the possibility of an increase in the risk of gastrointestinal cancers due to this drug.

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References

(1) Curtis RE, Boice JD Jr, Shiner DA, Hankey BF, Fraumeni JF Jr. Second cancers after ad-