Modulation of High-Dose Infusional Fluorouracil by Low-Dose Methotrexate in Patients With Advanced or Metastatic Colorectal Cancer: Final Results of a Randomized European Organization for Research and Treatment of Cancer Study

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Purpose: Methotrexate (MTX) has been described to modulate the activity of fluorouracil (5-FU) in patients with metastatic colorectal cancer. The European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group (GITCCG) conducted a phase III trial to investigate the efficacy and tolerability of the addition of low-dose MTX (40 mg/m²) to high-dose infusional 5-FU (60 mg/kg over 48 hours) given weekly for 4 weeks and thereafter every 2 (for 4 weeks) and 3 weeks.

Patients and Methods: Three hundred ten patients were randomized between 1987 and 1992. Eligible patients had measurable advanced or metastatic colorectal cancer and had not been pretreated with antifolates or fluorodinated pyrimidines. All 297 eligible patients were evaluated for survival; toxicity was assessed in 292 patients who received at least one course of treatment. Patients with bidimensionally measurable disease (n = 230) were also evaluated for response according to standard criteria.

Results: The addition of low-dose MTX to high-dose infusional 5-FU led to a doubling of the response rate from 10% to 21% (P = .025). The median survival time also increased from 9.3 to 12.5 months, but this difference was not statistically significant (P = .12). High-dose infusional 5-FU with or without low-dose MTX was well tolerated, with grade 3 to 4 toxicity in greater than 10% of patients only occurring for stomatitis with the combination treatment. Performance status was the sole prognostic factor for survival in a multivariate analysis.

Conclusion: Low-dose MTX effectively modulated high-dose infusional 5-FU in a large, randomized trial in which less than 5% of patients received leucovorin.


ONE OF THE FIRST drugs found to modulate the cytotoxic activity of fluorouracil (5-FU) was methotrexate (MTX). This drug inhibits dihydrofolate reductase, which leads to inhibition of purine synthesis and thereby increased levels of the phosphate donor phosphoribosylphosphate (PRPP). As a consequence, the intracellular formation of 5-FU nucleotides is enhanced, with increased incorporation of 5-FU into RNA and increased levels of fluorodeoxyuridine monophosphate (FdUMP), the inhibitor of thymidylate synthetase.6

In a number of in vivo and in vitro tumor models, MTX, if given before 5-FU, was indeed found to enhance 5-FU—induced cytotoxicity.7 Subsequent phase II trials in patients with metastatic colorectal cancer were summarized by Kemeny et al4 and Hermann et al,5 who showed that response rates of approximately 35% could be obtained with MTX doses as low as 40 mg/m² if MTX preceded 5-FU administration by at least 3 hours.

In 1986, the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group (GITCCG) decided to test the concept of modulation by MTX in a phase III trial. The trial was designed according to the principle to make the dose-intensity of the active drug (5-FU) as high as possible and that of the modulating drug (MTX) as low as possible.6 This would allow the best testing of biochemical modulation without the inherent tendency of the modulating drug to compromise the dose-intensity of 5-FU. Kemeny et al4 used 40 mg/m² of MTX followed 24 hours later by 600 mg/m² of 5-FU and found a response rate of 32%. Moreover, this dose of MTX could be given without leucovorin rescue, which made it unnecessary to introduce the bias of this, possibly, also modulating agent.7 Therefore, this dose of MTX was chosen for modulation.

Investigators from Vancouver8 pioneered a number of ways to administer 5-FU in continuous infusions of short duration but at frequent intervals. The best results (30% response rate) were obtained with 48-hour infusions of 60 mg/kg 5-FU given weekly. This approximates a dose-intensity of approximately 2.5 mg/m²/wk, which is con-
considerably higher than with any other schedule and close
to the maximal-tolerated dose of 5-FU (≈ 3.0 g/m²/wk). 9,10

Based on these rationales and after a pilot study of this
particular combination of low-dose MTX and high-dose
5-FU was performed, the phase III study was started in
1987. Interim data have been reported at several meetings;
this is the final report.

**PATIENTS AND METHODS**

**Eligibility Criteria**

Patients were eligible if they had advanced unresectable or meta-
static adenocarcinoma of the colon or rectum. The presence of ade-
ocarcinoma had to be histologically or cytologically documented,
preferably on a metastatic lesion or, if this was impossible, on the
primary tumor. In the latter situation, unequivocal clinical evidence
of a progressive lesion was required. Patients had measurable or
assessable disease that included lung metastases measurable in one
or two dimensions on x-ray, palpable nodules and nodes, hepatomeg-
aly if the inferior liver edge was palpated at 5 cm below the cortal
margin, and lesions visible on computed tomographic-scan or ultra-
sound that could be measured in at least one diameter. Lesions in
irradiated fields, effusions, bone metastases, malignant ulcers, and
changes in biochemical tests, including tumor marker levels, were
not considered measurable or assessable manifestations of disease.
Patients were less than 71 years of age; had a World Health Organi-
ization (WHO) performance status of 0, 1, or 2; and had adequate
liver (bilirubin level < 50 µmol/L), kidney (creatinine concentration
< 120 µmol/L), and hematologic (WBC count > 3,000/µL and platelet
count > 100,000/µL) function. Patients with a life expectan-
ty shorter than 3 months, previous chemotherapy with fluonodi-
lation with a fully implantable port system. In some institutions, pa-
tients using salicylates or other nonsteroidal antiinflammatory agents
were only eligible if the medications could be discontinued during treatment. Patients
with pleural or peritoneal effusions could only be entered if these
effusions were controlled to very small volumes before therapy
started.

**Randomization**

Patients were randomized by telephone call or through the Euro-
Code Network at the EORTC Data Center in Brussels, Belgium. Patients
were stratified by institution. They were randomized to re-
ceive one of the following regimens: (1) high-dose infusional 5-FU
or (2) the same 5-FU treatment plus low-dose bolus MTX.

**Chemotherapy**

5-FU treatment consisted of a continuous infusion of 60 mg/kg
over 48 hours in 5% glucose or dextrose. The drug could be given
through a peripheral line or through a central line, mostly in connec-
tion with a fully implantable port system. In some institutions, pa-
tients were admitted for this treatment, but in most cases, 5-FU was
given through a central line connected to an ambulatory pump. Four
courses were given at weekly intervals, and another four at 2-week
intervals. In case of stable or responding disease, treatment was
continued on an every-3-week basis until progression or unaccept-
able toxicity. According to randomization, half of the patients also
received MTX 40 mg/m² by intravenous push just before the start of
each 5-FU infusion. Doses and schedules of 5-FU were identical
to those in the other arm.

**Dose Modifications**

In case of a WBC count less than 3,000/µL, or neutropenia grade
1 or diarrhea grade 1 on the day before the start of infusion, treatment
was delayed for 1 week and restarted if the patient had recovered
at the same doses. In case of neutropenia greater than grade 1 or
diarrhea greater than grade 1, treatment was delayed for 1 week
and restarted at 75% of the 5-FU dose with leucovorin rescue 22.5 mg
orally every 6 hours for eight doses starting 24 hours after MTX.
Treatment was withheld if the serum creatinine concentration in-
creased to greater than 120 µmol/L. Patients with a more than 1 week
delay of treatment were taken off protocol. In case of retrosternal
discomfort, ECG and cardiac enzymes were obtained. If abnormal,
treatment was discontinued, if normal, the next course was given
with monitoring of ECG and cardiac enzymes.

**Disease and Treatment Evaluation**

Complete response was defined in the disappearance of all known
disease determined by two observations at least 4 weeks apart. Partial
response required a decrease by ≥ 50% in the sum of the product
of the largest perpendicular diameters of all bidimensionally measur-
able indicator lesions. It was not necessary for all lesions to have
regressed to qualify for a partial response, but no lesions should
have progressed and no new lesions should have appeared. Disease
progression was defined as a ≥ 25% increase in the size of at
least one measurable lesion or the appearance of a new lesion. The
occurrence of effusions was considered progression if the cytology
was positive. Patients who did not qualify for response or progression
were considered stable. Patients were assessable for response pro-
vided they had received 12 weeks of therapy or had been taken off
protocol because of progressive disease before that time. In the latter
situation, they were classified as having early progression. Patients
were assessable for toxicity provided they had received at least one
course of therapy. In a few instances, patients were declared not
assessable for efficacy or toxicity because of severe protocol viola-
tions as decided by the study coordinator. Partial and complete re-
sponses were evaluated extramurally.

**Statistical Considerations**

Randomization was centralized in the EORTC Data Center. Dur-
ing randomization, patients were stratified by institution. The ran-
donization was performed using the minimization technique. 11 As-
suming that the 1-year survival rate in the 5-FU arm is approximately
30%, a total of 308 patients (154 in each treatment arm) was neces-
sary to detect an increase to 45% in the 5-FU-MTX arm with a two-
sided type I error of 0.05 and a power of 80%. 12 Response rates
were compared using the χ² test for all patients who had a least one
bidimensionally measurable lesion at entry. Duration of response
was calculated from the date of progression. Survival curves were
estimated using the Kaplan-Meier technique. 13 Differences in the
duration of survival were compared using a two-sided log-rank test. 14
To adjust for confounding variables, the Cox proportional hazards
model 15 was used. Except for survival, which was based on all
randomized patients for whom any information was received after being randomized (all patients but one), all other analyses were based on all eligible and assessable patients.

Administrative Data

Between 1987 and 1992 310 patients were registered (Table 1). Thirteen (4%) were ineligible because of the absence of measurable or assessable disease (n = 7), incomplete or inadequate data (n = 4), or poor physical condition (n = 2). Five eligible patients were not assessable for toxicity because treatment was never started (n = 4) or lack of data (n = 1). Bidimensionally measurable lesions were present in 230 patients, who were therefore assessable for response. Survival data were available on all patients but one.

RESULTS

Patient Characteristics

Table 2 lists patient characteristics at entry per treatment arm. Seventy-six percent of patients were aged greater than 50 years; 67% had a rectosigmoid primary tumor site. Seventy-seven percent of patients had bidimensionally measurable disease at randomization. The large majority (89%) of patients had received surgery (curative or palliative) and only nine patients (3%) had received prior chemotherapy, mainly in the context of a phase II study with an experimental agent that was not an antifolate or fluoridated pyrimidine.

Tumor Response

In six patients in the high-dose 5-FU arm and eight patients in the low-dose MTX/high-dose 5-FU arm, response could not be assessed due to premature discontinuation of treatment (n = 10), major protocol violations (n = 2), or lack of data (n = 2). Table 3 lists tumor responses according to treatment in the remaining 216 patients with bidimensionally measurable disease. The response rate of low-dose MTX/high-dose 5-FU was superior to high-dose 5-FU (23% v 11%; P = .025). Similar results were obtained when the 14 patients who were not assessable for response were included in the analysis.
Survival comparisons have been performed on the basis of all randomized patients following an intent-to-treat policy. With 293 of 309 patients dead, the median survival time was 9.3 months for the high-dose 5-FU arm and 12.5 months for the low-dose MTX/high-dose 5-FU arm (Fig 1). This difference of 3 months is not statistically significant.

Adjustment for Prognostic Factors

A number of factors were analyzed for their impact on prognosis. Results from the univariate analysis are listed in Table 4. Only good performance status and prior surgery (in particular, curative surgery) were associated with a favorable prognosis. Multivariate analysis was applied to adjust for possible prognostic factors. Only performance status was retained in the model; patients with a performance status of 1 or 2 had a relative risk of 1.92 compared with those with a performance status of 0 ($P < .001$). Treatment was not a significant prognostic factor when adjusting for performance status ($P = .19$).

Toxicity

Side effects and toxicity for patients who received at least one cycle of treatment are listed in Table 5. Few patients suffered hematologic side effects. Four patients in each treatment arm had cardiac toxicity that consisted of angina pectoris in five, an episode of high blood pressure in one, and ECG changes in two. All symptoms were reversible. Four patients had cerebellar ataxia, of which one was grade 3 to 4. This occurred during early cycles (no. 1 to 5) and disappeared thereafter. A significant difference in favor of the high-dose 5-FU arm was observed for nausea and vomiting; however, even in the low-dose MTX/high-dose 5-FU arm, 45% of patients had no symptoms in this respect. The only other significant difference was the occurrence of stomatitis, which was virtually absent (10% grade 1 to 2) without but relatively frequent (43% grade 1 to 3) with MTX. This indicates that 40 mg/m$^2$/wk of methotrexate is close to the maximum dose that can be given in conjunction with high-dose 5-FU without the need for leucovorin rescue.

DISCUSSION

In this study, we found evidence for an enhancement of the treatment results of high-dose infusional 5-FU by the addition of low-dose MTX in patients with advanced inoperable or metastatic colorectal cancer. This enhancement was moderate in size and consisted of a doubling of the percentage of responding patients ($11\%$ vs $23\%$; $P$
Table 4. Duration of Survival Comparisons According to Possible Prognostic Factors

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>O/N</th>
<th>Median Survival (months)</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 58</td>
<td>143/148</td>
<td>12.5</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 58</td>
<td>139/149</td>
<td>10.0</td>
<td>1.02</td>
<td>0.81-1.30</td>
<td>.842</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>156/167</td>
<td>11.1</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>126/130</td>
<td>11.7</td>
<td>0.95</td>
<td>0.75-1.20</td>
<td>.690</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>192/204</td>
<td>12.1</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>90/93</td>
<td>8.8</td>
<td>1.09</td>
<td>0.64-1.40</td>
<td>.534</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>112/122</td>
<td>14.2</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>166/171</td>
<td>7.8</td>
<td>1.92</td>
<td>1.50-2.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>86/91</td>
<td>8.1</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>190/200</td>
<td>12.2</td>
<td>0.84</td>
<td>0.65-1.10</td>
<td>.204</td>
</tr>
<tr>
<td>Prior surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28/28</td>
<td>6.9</td>
<td>1.0</td>
<td></td>
<td>.038</td>
</tr>
<tr>
<td>Curative</td>
<td>131/139</td>
<td>13.2</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncurative</td>
<td>119/126</td>
<td>9.7</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28/28</td>
<td>6.9</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any surgery</td>
<td>250/265</td>
<td>11.9</td>
<td>0.6</td>
<td>0.39-0.98</td>
<td>.041</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>227/239</td>
<td>11.4</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51/54</td>
<td>10.4</td>
<td>1.15</td>
<td>0.85-1.59</td>
<td>.382</td>
</tr>
</tbody>
</table>

Abbreviation: O/N, observed/number of patients.

= .025) and a difference in the median survival time of 3 months (P = .12). These data show that a dose of MTX as low as 40 mg/m² can modulate the activity of high-dose infusional 5-FU.

The Advanced Colorectal Cancer Meta-Analysis Project¹⁶ identified seven other randomized trials that compared 5-FU alone with 5-FU plus MTX, and included another 868 patients.⁷,¹⁷,²² In three of these trials,¹⁷,²⁰,²¹ the response rate was significantly higher in the 5-FU/MTX arm; in no trial was the opposite true. The overall odds ratio for response was 0.51 (95% confidence interval, 0.37 to 0.70) for all trials, including EORTC 40872, which indicates a highly significant advantage for 5-FU/MTX (P < 10⁻⁴). For overall survival, only one study¹⁷ showed a significant advantage for 5-FU/MTX, but several other trials showed survival trends leading to an overall survival odds rate of 0.87 (95% confidence interval, 0.77 to 0.98; P = .024). These results did not change if prognostic information from a Cox regression model was taken into account.

Two of the modulations of 5-FU that have shown considerable in vitro activity have now been found to modulate 5-FU efficacy in patients as well.¹⁴,²³ The magnitude of the effects observed for leucovorin and MTX are about of similar size, with a doubling of the response rate (from ≈ 10% to ≈ 20%) and a nonsignificant (leucovorin) or small but significant (MTX) prolongation of survival. Direct comparisons between leucovorin- and MTX-modulated 5-FU treatment have been performed by the North Central Cancer Treatment Group (NCCTG) (5-FU/MTX v 5-FU/leucovorin in two doses²⁴), by three groups included in the meta-analysis (5-FU v 5-FU/leucovorin v 5-FU/MTX),⁷,¹⁹,²² and by the Nordic Gastrointestinal Tumor Adjuvant Therapy Group.²⁵ No differences in response rates were observed, with the exception that the extended NCCTG study found 5-FU/MTX (13% response rate) to be inferior to the other two arms (31% and 42% response rates). It should be noted, however, that only in that trial was the dose of 5-FU lower in the 5-FU/MTX group as compared to with 5-FU/leucovorin arms. It can be concluded that MTX and leucovorin are equally effective modulators of 5-FU in patients with metastatic colorectal cancer.

Our trial allowed the use of leucovorin in selected patients
with MTX-induced toxicity. In actual practice, less than 5% of the patients in the low-dose MTX/high-dose 5-FU arm received leucovorin, realizing one of the important goals of choosing a low dose of MTX. In some other trials included in the meta-analysis that used higher doses of MTX (≥ 200 mg/m²), leucovorin rescue was routinely given, mostly after the administration of 5-FU and in low doses. Some contribution of leucovorin to the results obtained with MTX/5-FU combinations in these studies cannot be excluded. However, the results of the EORTC provide strong evidence that MTX is also a clinically effective modulator without the addition of leucovorin.

If MTX and leucovorin each modulate 5-FU activity, but through different mechanisms, would it be useful to combine both agents to obtain double modulation? We performed a phase II study of high-dose infusional 5-FU combined with oral leucovorin during 5-FU infusion in a dose that should allow for leucovorin levels greater than 1 μmol/L. A response rate of 25% was obtained. Results from experimental models have suggested that three-drug combinations of 5-FU, MTX, and leucovorin are not superior to two-drug combinations or may even be antagonistic. One reason may be that MTX and leucovorin compete for the same reduced folate transport mechanism to enter the cell. Trimetrexate, an MTX analog, can enter the cell by simple diffusion and may be more suitable for combination with leucovorin. A phase I trial with this combination in patients with metastatic colorectal cancer has been performed with promising results.

The timing of the MTX administration is crucial for an optimal modulating effect in vitro. PRPP levels, thought to be the mean mediator of modulation, increase until a maximum after 24 hours. In clinical practice, intervals between MTX and bolus 5-FU greater than 3 to 4 hours have been found to be superior to shorter intervals. Marsh et al. directly compared MTX 200 mg/m² followed by 5-FU 600 mg/m² after 1 or 24 hours with leucovorin rescue 24 hours after MTX. With the 24-hour interval, response rate (29% vs 14%) and median survival time (15.3 vs 11.4 months) were clearly superior. In our trial, 48-hour continuous infusion rather than bolus 5-FU was applied. It was reasoned that with MTX given 24 hours before the start of 5-FU, PRPP levels would be the highest during the build up of 5-FU levels and probably be declining or normal again during most of the 5-FU administration. With MTX given at the start of the infusion of 5-FU, maximum PRPP levels can be expected in the middle of the infusion. Therefore, the scheduling of our trial is not contradictory to but in line with what is known from experimental and clinical data regarding the optimal interval.

### Table 5. Toxicity by Treatment Group According to WHO Criteria

<table>
<thead>
<tr>
<th>Toxicity/Grade</th>
<th>High-Dose 5-FU ( (n = 148) )</th>
<th>Low-Dose MTX/High-Dose 5-FU ( (n = 144) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1.37</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>3</td>
<td>2.05</td>
</tr>
<tr>
<td>3-4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>2</td>
<td>1.37</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1.37</td>
</tr>
<tr>
<td>Hepatic</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>4</td>
<td>2.71</td>
</tr>
<tr>
<td>Nausea and vomiting*</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>52</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>3.43</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1.37</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2.05</td>
</tr>
<tr>
<td>Stomatitis†</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>3-4</td>
<td>2</td>
<td>1.37</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Alopecia</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>3-4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>4</td>
<td>2.71</td>
</tr>
<tr>
<td>3-4</td>
<td>1</td>
<td>0.68</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*\( P = .03. \)
†\( P = < .001. \)

The combination of low-dose MTX and high-dose infusional 5-FU was well tolerated. Myelosuppression was negligible and the most prominent toxicity was stomatitis, which occurred in 43% of patients and was severe (grade 3 to 4) in 10%. This compares favorably with the incidence of severe diarrhea and myelosuppression reported for weekly bolus 5-FU with high-dose leucovorin and 5-day bolus 5-FU with low-dose leucovorin. The availability of central lines with a subcutaneous reservoir and reliable pumps has increasingly allowed treatment to be given entirely at home. As a consequence, in the newer EORTC studies, the 3-week interval with later courses has been changed to a 2-week interval and the period of weekly administrations has been lengthened without detrimental effects as far as toxicity is concerned. Provided appropriate infusional technology is available, high-dose infusional 5-FU is an attractive treatment that can be modulated by low-dose MTX.
REFERENCES

33. Kamen BA, Elbl B, Cashmore AR, et al: Uptake and efficacy of trimetrexate (TMQ, 2,4-diamino-5-methyl-6(3,4,5-trimethoxyani-


