Cellular but not Plasma Pharmacokinetics of Lometrexol Correlate with the Occurrence of Cumulative Hematological Toxicity

Timothy W. Synold, Edward M. Newman, Mary Carroll, Franco M. Muggia, Susan Groshen, Kay Johnson, and James H. Doroshow

Departments of Medical Oncology and Therapeutics Research [T. W. S., M. C., J. H. D.] and Pediatrics [E. M. N.], City of Hope National Medical Center, Duarte, California 91010; and Division of Medical Oncology, USC-Norris Comprehensive Cancer Center, Los Angeles, California 90033 [F. M. M., S. G., K. J.]

ABSTRACT

Lometrexol inhibits the first folate-dependent enzyme in de novo purine biosynthesis and is avidly polyglutamated and retained in tissues expressing folypolyglutamate synthetase. Although clinical studies have been limited by cumulative toxicity, preclinical studies show that pretreatment with folic acid can protect normal tissue while maintaining tumor cytotoxicity. Therefore, a Phase I study of lometrexol every 21 days preceded by i.v. folic acid was initiated. Lometrexol was studied in six patients at 15 mg/m², in six patients at 20 mg/m², in three patients at 25 mg/m², and in nine patients at 30 mg/m². Patients received either 5 mg of folic acid 1 h before or 25 mg/m² 3 h before lometrexol. Blood samples were obtained around the first course and weekly thereafter for determination of plasma and erythrocyte (RBC) lometrexol concentrations. Bioactive folates in plasma and RBCs were determined in a subset of patients. Lometrexol pharmacokinetics were best described by a three-compartment model. Mean clearance and volume of distribution were 1.6 ± 0.6 liters/h/m² and 8.9 ± 4.1 liters/m². Mean half-lives were 0.23 ± 0.1, 2.9 ± 1.4, and 25.0 ± 48.7 h. Pharmacokinetics were independent of either lometrexol or folic acid dose. In the weekly blood samples, RBC lometrexol levels rose, long after plasma lometrexol was undetectable. RBC lometrexol levels were independent of folic acid or lometrexol dose. Bioactive folates measured in plasma and RBCs during this same time period did not accumulate. Rising RBC levels were correlated with a fall in hematocrit, hemoglobin, and platelet count. This study indicates that the cumulative toxicity of lometrexol is related to tissue concentration and not plasma pharmacokinetics. RBC lometrexol may be an indicator of cumulative drug exposure and effect.

INTRODUCTION

Lometrexol [(6R)-5,10-dideaza-5,6,7,8-tetrahydrofolic acid] is an antifolate antimetabolite with a broad spectrum of cytotoxic activity against preclinical murine tumor model systems and human tumor xenografts (1, 2). Unlike classical antifolates, lometrexol acts by inhibiting glycinamide ribonucleotide formyltransferase, the first folate-dependent enzyme in the de novo purine biosynthetic pathway (1). In addition to its unique mechanism of action, lometrexol is an excellent substrate for FPGS3 and is avidly polyglutamated (1, 3). It has been demonstrated previously that the polyglutamates of lometrexol are more potent inhibitors of glycinamide ribonucleotide formyltransferase than lometrexol itself (4, 5). Furthermore, in addition to having a higher affinity for their target enzyme, polyglutamated anabolites are retained intracellularly for prolonged periods of time (3).

Because of promising preclinical activity, clinical trials of lometrexol began almost 10 years ago; however, the utility of lometrexol has been limited by serious toxicities (thrombocytopenia, leukopenia, and mucositis), which appear to be cumulative and long-lasting (6, 7). It has been speculated that this cumulative toxicity may be related to the formation and retention of polyglutamated anabolites, resulting in longer than expected drug exposures in certain target tissues. In a previous Phase I study of bometrexol (7), unpublished data indicated that RBC folate levels appeared to increase over time and remain elevated for months. Because the RBC folates in that study were measured using a commercially available assay that cross-reacts with lometrexol, it was hypothesized that lometrexol was accumulating in RBCs. Tissue levels of other antifolates, such as methotrexate in erythrocytes, have been used as a measure of long-term drug exposure (8).

Dietary folic acid supplementation has been shown to modulate lometrexol toxicity without diminishing antitumor activity in preclinical models (9). As a result, recent clinical trials of lometrexol have all included the use of either prior or concurrent folic acid treatment. One such trial using folic acid supplementation beginning 1 week prior and continuing for 1 week following lometrexol demonstrated that much higher lometrexol doses could be given without cumulative toxicity (10). However, due to concerns that overly aggressive folic acid supplementation might rescue tumor as well as normal tissues, the current study evaluating the administration of lometrexol every 3 weeks preceded by a single i.v. dose of folic acid was undertaken. Because of its delayed toxicity profile, prolonged

3 The abbreviations used are: FPGS, folylpolyglutamate synthetase; AUC, area under the concentration versus time curve.
pharmacokinetic and pharmacological monitoring of lometrexol were important correlates of this clinical trial.

**MATERIALS AND METHODS**

**Patients.** Patients with a histologically documented diagnosis of a solid tumor were eligible for this study if they met the following inclusion criteria: (a) age of ≥21 years, (b) life expectancy of at least 4 months and Karnofsky performance status of ≥60%, (c) no chemotherapy or radiation therapy for at least 3 weeks prior to study entry, (d) evidence of adequate renal and hepatic function, (e) evidence of adequate bone marrow function, and (f) ability to give voluntary informed consent. Patients were ineligible if they met any of the following exclusion criteria: (a) concurrent use of cytoxic therapy or multivitamins containing folic acid, (b) presence of partial bowel obstruction or inflammatory bowel disease, (c) concurrent treatment with allopurinol, (d) presence of active infection, (e) presence of active angina pectoris or other uncontrolled heart disease, or (f) presence of other uncontrolled medical or psychiatric condition.

**Treatment Protocol.** The starting dose level of lometrexol was 30 mg/m² by rapid i.v. injection repeated every 3 weeks. Patients originally received 5 mg of folic acid by rapid i.v. injection 1 h before escalating doses of lometrexol. Due to the occurrence of cumulative toxicity at the first dose level, lometrexol dose levels were subsequently lowered to 20 and then 15 mg/m². With the continued incidence of cumulative toxicity, the study was amended to increase the folic acid pretreatment dose to 25 mg/m² given 3 h before lometrexol. The amended folic acid dose and schedule were chosen based on previously published experience with plasma 5-methyltetrahydrofolate levels (11). With the revised folic acid pretreatment, the starting lometrexol dose was 15 mg/m². The dose was subsequently escalated in cohorts of three patients to levels of 20, 25, and 30 mg/m².

**Pharmacokinetic Sampling.** Peripheral blood samples were obtained from all patients around the first course at the following times: immediately prior to treatment and 5 and 30 min and 1, 2, 4, 6, 12, 24, and 48 h after lometrexol. Blood was drawn weekly thereafter for determination of both plasma and RBC lometrexol and bioactive folate concentrations for as long as a patient remained on study. Samples for plasma analysis were centrifuged, and 1-ml aliquots were transferred to tubes containing 1 mg of ascorbic acid. For the weekly blood samples, 0.5 ml of whole blood was removed prior to separation of plasma, diluted 1:10 with 0.1% ascorbic acid, and incubated for 30 min at 37°C to lyse the RBCs and cleave both the lometrexol and endogenous folate polyglutamates to monoglutamates (12). All samples were stored frozen at −70°C or colder until analysis. Ascorbic acid was added to all whole blood and plasma samples to prevent ex vivo oxidation of endogenous folates.

**Determination of Plasma and RBC Lometrexol.** Lometrexol in plasma and whole blood was determined using a previously published high-performance liquid chromatography assay (13). Briefly, following a solid-phase extraction step using cation-exchange cartridges, chromatographic separation was achieved isocratically across a phenyl column. Using UV and electrochemical detectors in series for low and high sensitivity, respectively, lometrexol was determined over the entire range of clinically achievable concentrations with a single injection. This method has a percentage recovery of >85% and a limit of quantitation of 20 ng/ml and is accurate and precise to within 5.5%.

**Determination of Plasma and RBC Bioactive Folates.** Bioactive folates in plasma and whole blood were determined using a previously published microbiological assay (14). The assay is based on the growth of Lactobacillus rhamnosus (ATCC 7469, NCIB 10463), formerly Lactobacillus casei. Previous investigators have shown that longer chain folate polyglutamates are inactive in the L. casei microbiological assay (15). Therefore, whole blood samples were first incubated in the presence of endogenous conjugase to convert folate polyglutamates to monoglutamates (12). Moreover, because lometrexol appeared to inhibit the growth of L. rhamnosus, even when hypoxanthine or inosine was added to the assay medium, an extraction method was devised to separate bioactive folates from lometrexol. Blood was processed for both plasma and whole blood analysis, as described previously for the determination of lometrexol. For plasma, 0.3 ml of sample was diluted with 0.6 ml of 0.1% ascorbic acid and 0.3 ml of 0.5 M acetic acid was added. For whole blood lysate, 0.1 ml of 0.5 M acetic acid was added to 1.0 ml of the lysate. The resulting pH was in the range of 4–5 for both plasma and whole blood lysate. Bakers- Bond C₁₈ columns (VWR Scientific, Cerritos, CA) were preconditioned with 3 ml of methanol, followed by 3 ml of distilled water and 3 ml of 0.1% ascorbic acid, without allowing the columns to dry. The acidified whole blood lysate and plasma samples were loaded onto preconditioned columns, and folates were eluted with 1.0 ml of 0.1% ascorbic acid and 10 ml of 7.5% acetonitrile in 0.1% acetic acid. The sample flow-through, ascorbate wash, and 10 ml of 7.5% acetonitrile in 0.1% acetic acid were pooled together. The pooled eluate for each sample was analyzed for total bioactive folates. The solid-phase extraction method developed for use in this study resulted in recovery of 81 ± 11% of 5-methyltetrahydrofolate from spiked samples.

**Pharmacokinetic Modeling.** Plasma lometrexol data were fit with either a two- or three-compartmental pharmacokinetic model using ADAPT II software (16). The compartmental model that best described lometrexol disposition was identified and used to determine the primary (e.g., $V_c$, $K_{10}$, $K_{12}$, $K_{21}$, $K_{13}$, and $K_{31}$) pharmacokinetic parameters. Secondary pharmacokinetic parameters ($Cl_{plasma}$, $V_d$, half-lives, and AUC) were derived from the model-generated primary parameters.

**Statistical Methods.** The Akaike Information Criterion (17) was used to identify the compartmental pharmacokinetic model that best described the disposition of lometrexol. Distribution of the pharmacokinetic parameters were expressed as means ± SD. For analysis of the plasma pharmacokinetic data, the natural logarithm transformation was used to correct for heteroscedasticity. After transformation, a general linear regression model was used to evaluate the association between each pharmacokinetic parameter and either the lometrexol or folic acid dose. Significance testing was done using an $F$ test based on the regression model, with $P < 0.05$ being considered indicative of a significant difference.
RESULTS

Patient Characteristics. Between March and December of 1995, 24 patients were entered into this study. There were 12 men and 12 women, whose tumor types included colorectal (n = 11), lung (n = 6), breast (n = 4), and miscellaneous (n = 3) cancers. Six patients each were treated with 15 and 20 mg/m² lometrexol, whereas three patients received 25 mg/m², and nine patients were treated with 30 mg/m². Of the patients treated with 15 and 20 mg/m² lometrexol, three received 5 mg of i.v. folic acid 1 h before whereas the other three received 25 mg/m² 3 h before the lometrexol. All of the patients treated at the 25 mg/m² dose level received 25 mg/m² of folic acid 3 h before the lometrexol. At the 30 mg/m² lometrexol dose level, three patients received 5 mg of i.v. folic acid 1 h before whereas the other six received 25 mg/m² 3 h before the lometrexol. As reported previously (18), dose-limiting toxicities were encountered on cycles 2 and 3 in most patients, regardless of the lometrexol dose level. Grade 3 and 4 toxicities included neutropenia, thrombocytopenia, anemia, mucositis, and fatigue. Anemia was the most common toxicity encountered, with 5 of 24 patients requiring transfusions.

Plasma Pharmacokinetics. First-dose lometrexol plasma pharmacokinetics were determined in all 24 patients entered on study. Fig. 1 shows representative plasma concentration versus time curves for each of three lometrexol doses. Lometrexol elimination showed a triexponential pattern of decay, and the pharmacokinetics were best described by a three-compartment model in 16 of 24 patients, according to the Akaike Information Criterion. As shown in Table 1, the mean AUC with increasing dose (Fig. 2).

Plasma Pharmacokinetics were determined in all 24 patients requiring transfusions. Curves were generated in ADAPT II using a three-compartment pharmacokinetic model.

Table 1. Plasma pharmacokinetics by lometrexol dose

<table>
<thead>
<tr>
<th>Lometrexol dose (mg/m²)</th>
<th>n</th>
<th>C_{sys} (liters/h/m²)</th>
<th>V_{sys} (liters/m²)</th>
<th>t_{1/2a} (h)</th>
<th>t_{1/2b} (h)</th>
<th>t_{1/2c} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>6</td>
<td>1.7</td>
<td>11.0</td>
<td>0.19</td>
<td>2.9</td>
<td>30.7</td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>1.4</td>
<td>6.8</td>
<td>0.25</td>
<td>2.9</td>
<td>7.9</td>
</tr>
<tr>
<td>25</td>
<td>3</td>
<td>1.4</td>
<td>10.2</td>
<td>0.22</td>
<td>2.9</td>
<td>6.5</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>1.7</td>
<td>8.5</td>
<td>0.24</td>
<td>2.8</td>
<td>38.7</td>
</tr>
</tbody>
</table>

a Number of patients per dose level.

b Total number of patients.

Mean ± SD.

Table 2. Effect of folic acid pretreatment on lometrexol plasma pharmacokinetics

| Pharmacokinetic parameter | 5 mg i.v. folic acid 1 h before lometrexol | 25 mg/m² i.v. folic acid 3 h before lometrexol | p
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{sys} (liters/h/m²)</td>
<td>1.7 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>0.30</td>
</tr>
<tr>
<td>V_{sys} (liters/m²)</td>
<td>8.8 ± 1.6</td>
<td>9.0 ± 5.1</td>
<td>0.54</td>
</tr>
<tr>
<td>t_{1/2a} (h)</td>
<td>0.2 ± 0.2</td>
<td>0.2 ± 0.4</td>
<td>0.86</td>
</tr>
<tr>
<td>t_{1/2b} (h)</td>
<td>2.1 ± 1.1</td>
<td>3.3 ± 1.4</td>
<td>0.05</td>
</tr>
<tr>
<td>t_{1/2c} (h)</td>
<td>32.1 ± 73.7</td>
<td>20.7 ± 27.2</td>
<td>0.43</td>
</tr>
</tbody>
</table>

a Mean ± SD.
b F test based on regression model.

Fig. 2. Relationship between lometrexol dose and AUC calculated by dividing the dose by the model-derived systemic clearance. Line was generated by linear regression analysis.
**RBC Pharmacokinetics.** Weekly RBC lometrexol data were available in all 24 patients enrolled on study, with a median follow-up of 39 days (range, 14–111). Fig. 3 shows the RBC lometrexol levels *versus* time for each patient receiving either 5 mg of i.v. folic acid 1 h before (Fig. 3A) or 25 mg/m² 3 h before (Fig. 3B) lometrexol. Although plasma lometrexol was undetectable in all patients within 72 h after a dose and remained undetectable throughout the follow-up period, RBC lometrexol levels measured in weekly blood samples rose between courses. RBC lometrexol levels were detectable starting at around 4 days following the first dose and continued to rise weekly in every patient. Furthermore, the rate and extent of apparent lometrexol accumulation in RBCs are independent of plasma pharmacokinetics and either the lometrexol or folic acid dose.

Although no relationship between plasma pharmacokinetics and toxicity could be identified, a significant linear relationship existed between the accumulation of lometrexol in RBCs and the percentage fall in hemoglobin, hematocrit, and platelet count. Fig. 4 shows the relationship between the measured RBC lometrexol level and the percentage fall in hemoglobin (Fig. 4A), hematocrit (Fig. 4B), and platelet count (Fig. 4C). The correlation coefficients between the change in RBC lometrexol and the fall in these hematological parameters were $-0.68$ ($P < 0.001$), $-0.66$ ($P < 0.001$), and $-0.33$ ($P = 0.002$), respectively. No clear trends or differences in these relationships could be identified when the different lometrexol dosage levels were compared.

**Plasma and RBC Bioactive folates.** Bioactive folates in plasma and RBCs were determined in a subset of six patients over the same time period as that for lometrexol. Although the data confirm that significantly higher plasma folate levels were achieved with the higher folic acid pretreatment dose (data not shown), analysis of weekly blood samples failed to show accumulation of folates in the RBCs. Fig. 5 demonstrates the failure of RBCs to accumulate bioactive folates in patients receiving either 5 mg or 25 mg/m² i.v. folic acid prior to lometrexol.

**DISCUSSION**

Initial Phase I studies of lometrexol demonstrated that drug-induced toxicity was related to the cumulative dose rather than the result of a single dose. These toxicities were severe and long-lasting, usually occurring following the second or third course of therapy (6, 7). Laboratory investigations performed after the initial Phase I studies found that lometrexol-induced
cumulative toxicity could be modulated by folic acid supplementation without affecting tumor cytotoxicity (9). As a result, subsequent clinical development of lometrexol has included various schedules of folic acid supplementation. One such study, consisting of daily doses of oral folic acid beginning 1 week prior to lometrexol and continuing for an additional week after, found that repeated courses of much higher lometrexol doses could be given safely (10). However, due to fears that folic acid may rescue tumor as well as normal tissue if the pretreatment regimens were too aggressive, we initiated a trial of lometrexol every 3 weeks, preceded by a single i.v. dose of folic acid. As reported previously (18), this trial was limited by the occurrence of cumulative and long-lasting hematological toxicities. Recognizing that lometrexol-induced cumulative toxicity might be due to prolonged tissue retention and delayed elimination, plasma and whole blood drug levels were measured in each patient throughout his/her clinical course in an effort to correlate the pharmacokinetics of lometrexol with toxicity.

The plasma pharmacokinetics of lometrexol in patients treated with and without folic acid supplementation have been described previously. Similar to our study, Wedge et al. (10) reported that lometrexol plasma pharmacokinetics were best described by a three-compartment pharmacokinetic model and that the pharmacokinetics were independent of lometrexol dose and folic acid supplementation. Moreover, lometrexol plasma clearance, volume of distribution, and elimination half-lives reported here are in good agreement with the results of Wedge et al. (10). Although this study confirms previous plasma pharmacokinetic findings, the determination that lometrexol accumulates and is retained in RBCs indicates a complex clinical pharmacology that may help to explain the unique toxicity profile of this agent.

Accumulation of lometrexol in RBCs was previously proposed because of unpublished reports of high RBC folate levels in patients receiving lometrexol. During an earlier Phase I trial of lometrexol, Ray and colleagues (7) found that weekly RBC folate levels increased over time and remained elevated for months. These investigators used a commercially available folate immunoassay that potentially cross-reacts with lometrexol. It was hypothesized that it was actually lometrexol that was accumulating in RBCs. Our study confirms this hypothesis by showing definitively that lometrexol levels in RBCs increase continuously over time and that this apparent accumulation is independent of either lometrexol or folic acid dose. Moreover, bioactive folates, as measured by a functional microbiological assay rather than by an immunoassay, did not accumulate over the same time period.

Once natural folate cofactors and antifolates enter mammalian cells, several glutamyl residues are added by FPGS. Increasing in vitro and clinical evidence indicates that polyglutamation by FPGS is central to the therapeutic activity of many cytotoxic antifolates. Although circulating RBCs have undetectable FPGS activity, purified normoblasts express very high levels of activity (19, 20). Therefore, it has been proposed that folates accumulate in normoblasts in the bone marrow as polyglutamates and are retained for the life of the cell. As a result, folate accumulation in erythrocytes, unlike plasma folates, is not influenced by recent dietary intake and better reflects the long-term folate (or antifolate) status of the host. Likewise, studies using age fractionated erythrocytes have concluded that methotrexate is incorporated in RBC precursors of the bone marrow (21).

The RBC lometrexol levels in this study were determined by taking the difference between the measured whole blood and plasma levels. Although lometrexol was undetectable in patients plasma starting 72 h after the dose, the whole blood concentrations continued to rise during the weeks between doses. It reasonable to assume, therefore, that the measured lometrexol was present primarily in the cellular fraction and that the increase over time probably reflects the maturation and release from the bone marrow of hematopoietic cells, which were loaded with long chain lometrexol polyglutamates. Moreover, it is likely that the intracellular lometrexol was present in the RBCs in its polyglutamated form, and through the action of endogenous plasma conjugase, the polyglutamates were converted to monoglutamate prior to high-performance liquid chromatography analysis. Although this hypothesis could have been tested, we were unable to perform the necessary experiments because all of the whole blood samples were incubated with endogenous conjugase at the time of collection.
Although lometrexol plasma pharmacokinetics were not related to the occurrence of any toxicity, RBC lometrexol levels were correlated with the percentage fall in hemoglobin, hematocrit, and platelet count. Because anemia requiring transfusions was the most commonly encountered toxicity on this Phase I study, usually occurring following course two or later, it is possible that the occurrence of delayed-onset anemia is a result of the accumulation of lometrexol in the RBCs. Although it is not clear why RBC lometrexol levels are related to delayed toxicity, one possibility is that the RBCs are acting as a drug reservoir. As drug-loaded RBCs lose membrane integrity over time, lometrexol may be slowly released back into the circulation. However, we were unable to detect lometrexol in plasma more than 72 h after i.v. administration during this study, even at the times corresponding to the highest RBC concentrations. Because the assay used to examine lometrexol levels in this study has a lower limit of detection of 10 ng/ml, it seems unlikely that delayed toxicity is due to prolonged exposure to circulating drug in plasma.

Yet another possible explanation for the correlation between RBC lometrexol levels and delayed toxicity is that the RBCs could be acting as a surrogate tissue for the true site of action. Lometrexol may be accumulating in other tissues, particularly those in which toxicity is occurring, in parallel to the increases seen in RBCs. Finally, it is possible that the increase in RBC lometrexol levels and the observed decreases in hemoglobin, hematocrit, and platelets, although they occur in parallel, are unrelated. The cumulative anemia could be the result of folate deficiency caused by depletion of total body folate stores by lometrexol. This would explain why trials of lometrexol that included daily folic or folic acid supplementation were able to give much higher doses safely (10, 22). However, lometrexol-induced folate deficiency as the cause of the chronic anemia appears unlikely in this case because we did not see a decrease in either plasma or whole blood folates in any of the patients studied. Therefore, the most probable explanation for the cumulative anemia seen on this study is the direct effect of intracellular lometrexol polyglutamates on RBC production.

Persistent intracellular levels of methotrexate have long been reported in the erythrocytes and livers of patients receiving chronic therapy (23, 24). Moreover, the cellular accumulation of methotrexate has been associated with a concomitant loss of folates (24). As a result, it has been suggested that persistent methotrexate concentrations and/or the resulting folate deficiency is responsible for methotrexate-associated chronic toxicity. In children with acute lymphocytic leukemia, accumulation of methotrexate in erythrocytes as polyglutamates also serves as an indicator of overall methotrexate exposure during the maintenance phase of therapy and has been reported to correlate with survival (25). Several prospective studies have used erythrocyte methotrexate levels as an index of chronic drug exposure and as a method of assessing patient compliance (8, 26, 27).

This study is the first to definitively show that lometrexol accumulates in RBCs. It is likely that lometrexol, similar to methotrexate, accumulates as the polyglutamates in RBC precursors in the bone marrow. The apparent rise in peripheral RBC lometrexol levels probably reflects maturation and release of drug-loaded RBCs into the circulation. The demonstration that this apparent accumulation in RBCs is independent of dose indicates that lometrexol tissue uptake is limited by either transport or FPGS. Unlike plasma levels of lometrexol, RBC lometrexol concentrations correlate with the occurrence of cumulative hematological toxicity. Although it remains to be seen whether there is actually a causal relationship between RBC lometrexol and toxicity, the RBCs levels may serve as an indicator of general tissue uptake and retention and, therefore, may be useful as a predictor of delayed toxicity. In addition to methotrexate and lometrexol, several new agents that are substrates for FPGS are in various stages of development. It is quite possible that, as with lometrexol, plasma pharmacokinetics will not be the best measure of drug exposure for these agents that exhibit prolonged tissue retention.

REFERENCES
Cellular but not plasma pharmacokinetics of lometrexol correlate with the occurrence of cumulative hematological toxicity.

T W Synold, E M Newman, M Carroll, et al.

Clin Cancer Res 1998;4:2349-2355.

Updated version Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/4/10/2349

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.