Re: Severe Interaction Between Methotrexate and a Macrolide-like Antibiotic

In the Journal, Thyss et al. (1) reported that co-administration of high-dose methotrexate and the macrolide-like antibiotic pristinamycin resulted in prolonged elimination of methotrexate and subsequent severe mucositis and neutropenia. Because there is structural similarity between the new immunosuppressive agent tacrolimus and macrolide antibiotics, a similar interaction is of potential concern when this agent is administered with methotrexate. In addition, Kortsanje (2) reported that the combination of cyclosporine and methotrexate prolongs the elimination of both drugs and recommended that the combination be avoided. Despite the potential for drug interactions, low-dose methotrexate is used in the bone marrow transplant setting with cyclosporine to prevent graft-versus-host disease and is being investigated with tacrolimus (3-5).

We evaluated methotrexate concentrations following low-dose therapy given with cyclosporine or tacrolimus in six allogeneic bone marrow transplant patients (four patients with CML and two with AML). All patients signed a written consent approved by the institutional review board and received the same supportive care therapies and conditioning regimen of busulfan, cyclophosphamide, and cytarabine. Three patients received cyclosporine (3 mg/kg per day) by continuous infusion, and three patients were administered tacrolimus (0.03 mg/kg per day), starting the day before bone marrow infusion. All patients received methotrexate (15 mg/m²) on the first day following bone marrow transplantation (day +1). They received methotrexate (10 mg/m²) on days +3, +6, and +11. Blood samples were obtained from the patients 24 hours after each methotrexate dose and analyzed for methotrexate concentration by fluorescent photometry immunoassay (TDx; Abbott Laboratories, Chicago, IL) with a detection limit of 0.02 μM. Folinic acid rescue (5 mg administered orally or intravenously every 6 hours x 4 doses) was initiated 24 hours after days +3, +6, and +11 of methotrexate administration.

Of the 19 samples obtained, all concentrations except one were below 0.05 μM, with 50% of the concentrations being nonmeasurable (Table 1). In one patient who was administered cyclosporine, the concentration of methotrexate on day +12 was 0.06, but it was below detection limits on day +13 following administration of folic acid. Toxic effects, including duration of neutropenia and mucositis, were similar between patients treated with cyclosporine and tacrolimus and to those toxic effects reported by Storb et al. (4).

In our series, 95% of the methotrexate concentrations obtained 24 hours following a dose remained below the range recommended for administration of folic acid rescue (<0.05 μM) (6). In another report, Nevil et al. (7) found that folic acid rescue decreased hematologic, gastrointestinal, and hepatic toxic effects in bone marrow transplant patients receiving low-dose methotrexate with cyclosporine, even when methotrexate concentrations were less than 0.05 μM. Given the low and often nonmeasurable concentrations achieved, it is difficult to make any correlation between methotrexate concentrations and regimen-related toxicity. When low doses of methotrexate are used, the detection of drug interactions may also be confounded by the limited ability of assays to detect concentrations in the range of 0.01-0.05 μM.

In bone marrow transplant patients receiving low-dose methotrexate with cyclosporine or tacrolimus, we found methotrexate concentrations obtained 24 hours after a dose was administered did not significantly alter clinical care. We now routinely administer folic acid rescue following administration of methotrexate and obtain concentrations only if patients have risk factors for prolonged elimination or toxicity of methotrexate, such as renal failure, ascites, or pleural effusion. While it is possible that an interaction between methotrexate and cyclosporine or tacrolimus may occur, we believe that this interaction, if any, in bone marrow transplant patients is of no clinical significance.

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References


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<th>Table 1. Methotrexate concentrations*</th>
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<td><strong>Concentrations of methotrexate 24 h after dose, μM</strong></td>
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<tr>
<td>Patient No.</td>
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<td>1</td>
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*Comparison of methotrexate concentrations 24 hours after a dose in six bone marrow transplant patients receiving tacrolimus or cyclosporine in combination with low-dose methotrexate.


Note

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Paclitaxel in Doxorubicin-Resistant Metastatic Breast Cancer Patients

The report by Dr. Gianni and colleagues (1) made interesting and informative reading. The authors stress the safety and efficacy of paclitaxel (Taxol) in breast cancer patients resistant to doxorubicin and suggest that paclitaxel in combination with doxorubicin should be investigated in metastatic breast cancer. In this regard, we would like to draw their attention to some further data on taxanes relating to the subject.

Seidman and colleagues (2) treated patients with metastatic breast cancer resistant to anthracyclines with paclitaxel at a dose of 250 mg/m² infused over 24 hours. Of 76 patients, 25 (33%) had a major objective response, and the median duration of response was 7 months. Responses were more frequent in patients with primary anthracycline resistance (11 [30%] of 37 patients) as in those with acquired anthracycline resistance (10 [32%] of 31 patients), leading the authors to conclude that paclitaxel was effective therapy in patients with metastatic breast cancer resistant to anthracyclines.

Ravdin et al. (3) reported that a combined analysis of the two American trials of docetaxel (100 mg/m² infused over 1 hour every 3 weeks) as second-line therapy after anthracycline resistance yielded an overall response rate of 48% in 83 patients. Moreover, high response rates were seen in patients with unfavorable conditions, such as multiple disease sites (45%), visceral disease sites (46%), and liver involvement (34%); neutropenia was the primary toxic effect.

Simultaneous administration of paclitaxel and doxorubicin by 72-hour continuous infusion was studied in previously untreated metastatic breast cancer patients and yielded an overall response rate of 72% (8% of the patients had a complete response, and the median response duration was 9 months) (4). No alterations in paclitaxel or doxorubicin pharmacokinetics were observed when the drugs were administered alone versus in combination.

Sledge et al. (5) examined a regimen that alternated paclitaxel (200 mg/m²) and doxorubicin (75 mg/m²) every 3 weeks in patients with advanced breast cancer who had received no more than one prior chemotherapy regimen; objective responses were seen in 12 patients, and the median response duration was 11 months. These investigators also used concurrent doxorubicin (50 mg/m²) and paclitaxel (150 mg/m² infused over 24 hours) and found that doxorubicin followed by paclitaxel led to less mucositis than when paclitaxel was given first (5). Of 12 patients, five responded to treatment (two patients had a complete response and three patients had a partial response; the median response duration was 11 months). Based on these findings, the Eastern Cooperative Oncology Group is currently conducting a three-arm study with doxorubicin alone (60 mg/m² every 3 weeks) versus paclitaxel alone (175 mg/m²) versus doxorubicin (50 mg/m²) followed 4 hours later by paclitaxel (150 mg/m² infused over 24 hours).

The data above, in addition to the study by Gianni et al. (1) of paclitaxel administered by 3-hour infusion, represent progress in the management of metastatic breast cancer.

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References


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More About: a Prospective Study of Endogenous Estrogens and Breast Cancer in Postmenopausal Women

As Principal Investigator of the New York University (NYU) Women's Health Study from July 1984 to January 1994 and a co-author of the recently published paper (1) on estrogens and the risk of breast cancer, I feel obliged to comment on the news reports by David Holzeman (2,3) and to respond to the letter to the editor by Drs. Kuller and Gutai (4).

Holzeman (2) states that "Paolo Toniolo, M.D., of New York University School of Medicine, banked blood samples from 15,000 women in 1985, and is only now beginning to get results." To set the record straight and to give credit where credit is due, it should be noted that the initial planning and motivation for the NYU Study were due to the collaboration of Richard Bulbrook of the Imperial Cancer Re-