believe that this treatment schedule is worth testing in patients with other cancers in which a biologic activity of retinoids is involved.

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(7) Nappi S, Pagano O, Cavalli F. Metabolism of lometrexol, an inhibitor of de novo purine synthesis, is complicated by severe stomatitis and cumulative pancytopenia (I-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 (6-11); 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 pretreat 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, 25, 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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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, examining the levels of lometrexol in 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.

References


Notes

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