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Letter to the editors

Low-dose methotrexate therapy for hepatoblastoma

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Sir,

Historically, the treatment of hepatoblastoma has focused on surgical resection, with chemotherapy reserved for preoperative volume reduction and the prevention of metastases. Recent studies employing cisplatin-based chemotherapy have shown high initial response rates and longer periods of disease control [2, 3, 9]. However, tumor recurrence remains a major problem.

Methotrexate has been used in adults with hepatocellular carcinoma [1, 4, 10], but experience with this antifol in childhood hepatoblastoma is extremely limited [8]. One child with "malignant hepatoma" had complete regression of multiple pulmonary lesions after two courses of methotrexate. Evaluation of its efficacy has been limited by different routes of administration, dosing regimens and concurrent use of multiple anticancer agents.

We report on the use of low-dose methotrexate (LDMTX) in four children with hepatoblastoma who failed conventional therapy with a cisplatin-based regimen. The age range was from 5 months to 3 years, with equal distribution between males and females. Tumors were equally divided between fetal or mixed fetal/embryonic and macrotrabecular histology. All patients had previously undergone partial surgical resection of their tumors prior to starting methotrexate. Patients received weekly oral methotrexate, 7.5 mg/m^2 every 6 h for eight doses. The number of doses was adjusted downward by increments of two for severe mucositis or bone marrow suppression. Routine monitoring of renal, hepatic and bone marrow function was performed. Tumor response was judged by changes in alpha fetal protein concentrations (AFP, ng/ml) and confirmed by radiographic studies whenever possible.

Dramatic reduction in AFP concentrations were noted in two patients with nonmetastatic disease. During approximately 8 weeks of LDMTX therapy their AFP concentrations decreased from 300055 and 1530600 to 15000 and 4388, respectively. While both patients eventually died (pt 1 of *Pneumocystis* pneumonia and pt 2 of gastrointestinal hemorrhage), neither had evidence of viable tumor or metastatic disease at autopsy. Two other patients, both with metastatic pulmonary disease, also received LDMTX. Methotrexate in one patient was stopped after 2 weeks because of a rising AFP concentration. This patient eventually died of progressive disease. The other patient had stable AFP concentrations but developed recurrent lung disease after 4 months of LDMTX therapy. Following lung wedge resection this patient is alive and LDMTX therapy has been discontinued. The methotrexate toxicity observed in these patients included mucositis, which occasionally resulted in cancellation of several courses of therapy, and bone marrow suppression.

We observed successful use of LDMTX, as judged by declining AFP concentrations and lack of viable tumor at autopsy, in two out of four patients with hepatoblastoma failing standard multiagent chemotherapy. Both patients had biopsies consistent with fetal or mixed fetal and embryonic histology.

Since methotrexate accumulates in human and animal hepatic tissues following chronic low-dose therapy and also undergoes extensive entero-hepatic cycling, this agent may prove useful in the treatment of hepatoblastoma [5, 6, 11]. Both patients who failed LDMTX had metastatic disease to the lung and macrotrabecular tumor histology. Theoretically, pulmonary lesions may be less responsive, since they may not be exposed to equivalent drug concentrations or may exhibit differential drug sensitivity [7]. In this regard higher doses might be more effective, although toxic.

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