Correspondence

The Effects of Cyclosporine on the Pharmacokinetics of Doxorubicin in Patients with Small Cell Lung Cancer

Rushing et al.[1] present an interesting argument for the use of cyclosporine in an attempt to overcome clinical presentations of multiple drug resistance (MDR). Doxorubicin and cyclosporine are combined in patients with small cell lung cancer to overcome MDR. Increased P-glycoprotein production, a result of activation of the MDR1 gene, is modified by the actions of cyclosporine. Reduction of P-glycoprotein levels results in greater tumor concentration of doxorubicin and enhanced cytotoxicity. Trials of doxorubicin encapsulated in polyethylene glycol liposomes have shown greater target efficacy in the form of drug concentration at the tumor site, and reduced cytotoxicity to nontumor cells.[2] It is suggested that this mechanism is specific to MDR cells and does not result in increased cytotoxicity to nontarget cells.[3] Liposomal doxorubicin may overcome the problems of cytotoxicity; however, cyclosporine used alone and in combination with other agents should be investigated.

Suppression of the MDR1 gene is of major importance. The P-glycoprotein is active in MDR against agents employed in therapy for cancer and Acquired Immunodeficiency Syndrome. Gene therapy may be a key factor in research to overcome drug resistance. P-glycoprotein is believed to have arisen from the fusion of two independently evolved proteins. Changing the transcriptional process or the structure of the MDR1 gene with an agent that directly binds to P-glycoprotein might prevent excess P-glycoprotein production. Phenothiazines bind to the P-glycoprotein of isolates of human neuroblastoma cells.[4] Cyclosporine or verapamil, when used in combination with taxol, lowers the threshold of expressed MDR1 in myeloid leukemia cells in vitro.[5]

There is urgent need for effective therapies designed to target the MDR1 gene, whether by suppression of P-glycoprotein or alteration of MDR1 itself. In an era characterized by disease resistance to the most promising agents, the search for alternative therapies continues to be of importance.

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Reply

Mr. Randolph A. Klaff emphasizes the importance and need for new therapies against multidrug resistant (MDR) tumors. We are in agreement with this as well as with his statement that "There is urgent need for effective therapies designed to target the MDR1 gene, whether by suppression of P-glycoprotein or alteration of MDR1 itself." Although liposome-encapsulated doxorubicin and gene therapy may prove in the future to produce reduced cytotoxicity to nontumor cells while providing enhanced efficacy at the MDR tumor site, these options were not clinically available at the beginning of our trial.

As mentioned in his letter, one method of overcoming MDR is modification of the P-glycoprotein, either by preventing excess expression or through direct binding. Cyclosporine modifies MDR by binding directly to the P-glycoprotein, resulting in competitive inhibition of doxorubicin efflux from the tumor cell. Thus, we and several other investigators have explored the clinical feasibility of combining cyclosporine and doxorubicin in patients who are no longer responding to chemotherapy secondary to MDR.[1–3]

The increased toxicity observed when patients received cyclosporine with a doxorubicin course is believed to be attributable to the pharmacokinetic drug–drug interaction between the two agents, resulting in an increased systemic exposure [e.g., area under the serum concentration-time curve, (AUC)] of both doxorubicin and its major metabolite, doxorubicinol.[1] Similar to the management of other pharmacokinetic drug–drug interactions, coadministration of these agents will require dosage reduction of doxorubicin to prevent elevated serum concentrations.[2,3] However, we cannot say without a doubt that high dose cyclosporine and/or the other concurrently administered cancer chemotherapy (e.g., cyclophosphamide, vincristine, or their metabolites) did not contribute to the observed toxicities.

As stated at the end of our paper, the use of cyclosporine for modulation of MDR remains experimental and should be used only for MDR modulation in clinical trials.[1] Further studies are needed in which the dose of doxorubicin is modified

when given with high dose cyclosporine to understand better the contribution of cyclosporine to MDR modulation and the increased toxicity observed.

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Myelopathy after Intrathecal Chemotherapy: A Case Report with Unique Magnetic Resonance Imaging Changes

We read with interest McLean et al.'s paper.[1] Transient or permanent paraplegia after intrathecal (IT) chemotherapy in patients with leukemia or lymphoma is a seldom-described complication. Recently, we reviewed 35 cases reported in the literature (a table and references are available from Dr Ferris). McLean et al. have had three patients with this condition in the last few years. It seems that there should be more patients, but they have not been communicated. The lack of knowledge about the etiologic factors, including the disease's mechanism of action, and the absence of ancillary diagnostic explorations, should prompt future reports. To elucidate the role of preservative-free IT chemotherapy, the importance of reporting those patients whose disease does not involve the central nervous system (CNS) and who have not received radiotherapy should be especially stressed.

To our knowledge, McLean et al.'s patient is the second studied with magnetic resonance imaging (MRI).[1,2] They described a unique pattern of postgadopentetate dimeglumine enhancement limited to the lateral columns of the spinal cord in one of the three patients they attended. The MRI changes seen may be unique only because of the small number of patients explored with this technique.[2]

We managed a 6-year-old girl with common acute lymphoblastic leukemia without CNS involvement. Induction therapy included vincristine, daunorubicin, prednisone, and L-asparaginase. Two IT instillations of methotrexate (MTX), cytosine arabinoside (ara-C) and hydrocortisone were administered. She achieved complete remission, after which CNS prophylaxis was initiated. The first 2 months of prophylaxis included 24-hour pefusion of intermediate dose intravenous MTX (200 mg/m^2 intravenous bolus injection followed by 1000 mg/m^2 24-hour perfusion) plus triple IT chemotherapy every other week for a total of four courses, alternating with oral MTX every 2 weeks, and daily oral 6-Mercaptopurine.Two weeks after the second course of intermediate-dose intravenous MTX and triple IT chemotherapy, she developed progressive ascending myelopathy. CNS infection, leukemic relapse, and inadvertant drug overdosage were ruled out. Cerebrospinal fluid analysis revealed high protein content (121 mg/dl), no blast cells, myelin basic protein (MBP) 5,4 mg/ml, negligible MTX level, and negative serology for cytomegalovirus, varicella-zoster, herpes simplex type I, Epstein–Barr virus, HIV, and Toxoplasma gondii. An early MRI, performed within a week of the presentation of neurologic deficit, was normal. Six months later, MRI showed mild brain atrophy, and marked cerebellar and spinal cord atrophy on T1-weighted images; no abnormal signal intensity in the spinal cord was found on T2-weighted images. There are some poorly discussed points in McLean et al.'s patient. Both meningeal leukemia and CNS radiotherapy may contribute to neurologic deterioration, as McLean et al. illustrate. Thus, naming IT chemotherapy as the unique etiologic factor may be questioned. Moreover, further gait improvement with IT MTX may indicate that MTX is not the causative agent of myelopathy, ara-C being its ultimate cause. It seems more likely that CNS radiotherapy and CNS leukemia could have contributed to the development of paraplegia.

Neuropathologic examination of patients who have died supports the hypothesis of a direct toxic effect of IT chemotherapy. The primary targets of IT chemotherapy are the neurons, with secondary myelin breakdown.[3] Titration of cerebrospinal fluid MBP has been postulated as an early diagnostic tool and follow-up procedure.[4] However, an increased level of MBP has been observed only after the beginning of symptomatology.[3]

Imaging studies performed in reported cases include computed tomography (CT) and MRI. In addition to McLean et al.'s patient, imaging changes have been observed in two other patients, including the patient presented.[3] Von der Weid described normal CT of CNS performed within 1 week of the beginning of neurologic deterioration; and multifocal hypodensities in a following exploration performed 24 days after initial symptoms.[3] In our patient, early CT was also normal. Generalized CNS atrophy observed in MRI may represent the final outcome of early changes described by McLean et al. We wonder whether MRI was performed by McLean et al. when