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Short communication

Intrathecal administration of etoposide in the treatment of malignant meningitis: feasibility and pharmacokinetic data

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Summary. Two patients presenting with malignant meningitis resulting from small-cell carcinoma of the lung and with lymphoblastic leukemia, respectively, were treated by intrathecal administration of etoposide. In both cases, this treatment was well tolerated and produced relief of the central nervous system symptoms. Pharmacokinetic data showed that cerebrospinal fluid drug levels of up to 5.2 μg/ml were achieved, which were considerably higher than those obtained after i.v. administration of high-dose etoposide.

Introduction

The prognosis of patients presenting with neoplastic infiltration of the meninges from either solid tumors or hematological malignancies is usually poor [1, 8]. Many of these individuals receive chemotherapy through an intraventricular catheter or via repeated intralumbar infusions in the presence or absence of concurrent irradiation of symptomatic regions of the neuraxis. Few chemotherapeutic agents have been given for intrathecal therapy of malignant meningitis, among which methotrexate is most commonly used. Cytosine arabinoside (ara-C), thiotepa, L-asparaginase, and bleomycin have been less frequently given intrathecally [2]. A common disadvantage of these agents is their minor activity against nonhematologic malignancies. Patients presenting with lymphocytic leukemia often receive methotrexate or ara-C as prophylactic intrathecal treatment. The emergence of drug resistance and the severe neurologic toxicity of these agents have led to an increasing need for further investigation of chemotherapeutic agents that might be used intrathecally. We report the results of intraventricular administration of etoposide to two patients exhibiting malignant meningitis from small-cell lung cancer (SCLC) and acute lymphoblastic leukemia, respectively.

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Patients and methods

Patients

Case 1. A 55-year-old man was admitted to the hospital because of diplopia, paresis of the right leg, and symptoms of cauda equina syndrome. This patient had been diagnosed 19 months previously as having limited-disease SCLC, for which he had been treated with six courses of combination chemotherapy consisting of 45 mg/m^2 doxorubicin given i.v. on day 1; 1,000 mg/m^2 cyclophosphamide given i.v. on day 1; and 100 mg/m^2 etoposide given i.v. on days 1, 3, and 5. After a complete response had been achieved, radiotherapy was delivered to the chest in combination with prophylactic brain irradiation (30 Gy). At admission, computerized tomography (CT) of the brain revealed no abnormalities. A lumbar liquor sample was obtained and malignant cells were found in the cerebrospinal fluid (CSF). The neuron-specific enolase (NSE) concentration was 27.7 μg/l. The NSE level in serum that had been taken at the same time was 6.4 μg/l. There was no sign of a relapse of SCLC outside the central nervous system (CNS).

An intraventricular drain connected with an s.c. reservoir was placed and treatment was started. Therapy consisted of 0.5 mg i.v. etoposide formulation diluted in 2 ml saline, which was given intraventricularly once daily for 5 days, followed 21 days later by a second course of 0.5 mg etoposide given twice daily separated by an interval of approx. 2 h for 5 days. No therapy-related side effect was observed. After two courses of treatment the paresis of the right leg and the signs of cauda equina syndrome had improved. The CSF contained no malignant cells, and the NSE level in the CSF had normalized. The patient experienced a clinical CNS relapse 6 weeks thereafter. No further treatment was given, and the patient died 2 weeks later.

Case 2. A 42-year-old man presented with headache and pain in both arms and legs. A physical examination disclosed mild paraplegia and splenomegaly. At 16 months previously, lymphoblastic transformation of Philadelphia-chromosome-positive chronic myelocytic leukemia had been diagnosed. Treatment had involved induction chemotherapy consisting of 1.5 mg/m^2 vincristine given i.v. on days 1, 8, 15, 22, and 29; 45 mg/m^2 daunorubicin given i.v. on days 1–3; 10,000 IU/m^2 L-asparaginase given i.v. on days 1, 3, 5, 7, 9, 11, and 13; and 60 mg/m^2 prednisone given orally on days 1–28 and tapered to zero over days 29–35. This therapy was followed by three subsequent 8-week cycles of

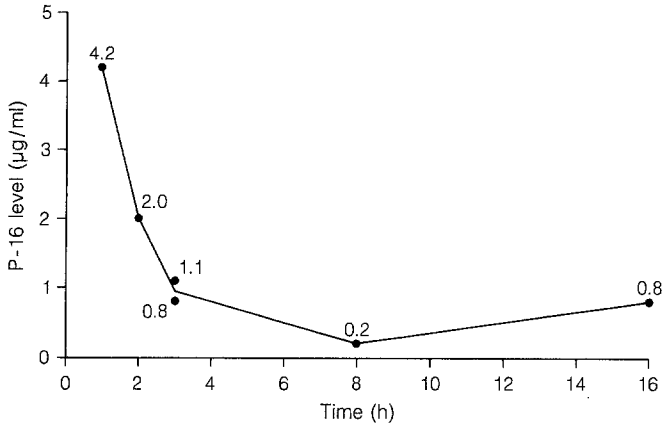

Fig. 1. Curve calculated for the elimination of etoposide in CSF in patient 2

high-dose (2,000 mg/m^2) ara-C given i.v. every 12 h on days 4 and 5 in combination with 120 mg/m^2 m-AMSA given on days 1–5, 10 mg/m^2 mitoxantrone given i.v. every 12 h on days 4 and 5, and 100 mg/m^2 etoposide given every 12 h on days 4 and 5. During the induction and consolidation phases, the patient had received CNS prophylaxis consisting of ten intrathecal injections of 15 mg methotrexate plus 4 mg dexamethasone separated by intervals 4 weeks. A complete remission was achieved.

At admission, the CSF contained lymphoblastic cells and treatment was instituted. Therapy consisted of 0.5 mg i.v. etoposide formulation diluted in 2 ml saline given intrathecally once daily for 5 days, followed 3 weeks later by the administration of 0.5 mg etoposide twice daily separated by an interval of 12 h for 5 days. No treatment-related side effect was observed. At cytological examination following two courses of treatment, the CSF was free of leukemic cells. Immunological analysis of antigenic surface-membrane markers specific for this patient's leukemia cells (CD10, CD19, CD22, TdT) revealed no leukemia cells in the cytospin. The paraparesis had disappeared. After a CNS response had been obtained, the patient was further treated with systemic chemotherapy consisting of mitoxantrone and etoposide. He died 9 weeks later of respiratory insufficiency in the presence of profound pancytopenia, with no sign of a CNS relapse being evident.

Methods

After 2 ml CSF had been drained from the s.c. reservoir and discarded, 2-ml samples were drawn for analysis of etoposide levels. Subsequently, 0.5 mg etoposide diluted in 2 ml saline was injected into the reservoir dome, and the reservoir was flushed with 2 ml saline. All CSF samples were immediately frozen and stored at –20° C until analysis. After the samples had been thawed, 1 ml liquor was extracted with 2×3 ml chloroform following the addition of the internal standards teniposide (VM-26) and tritiated etoposide (900 mCi/mmol) at a total volume of 50 µl. The chloroform layer was dried under nitrogen, and the residue was reconstituted in 75 µl methanol and diluted with 75 µl water. Of each sample, 100 µl was analyzed by high-performance liquid chromatography (HPLC).

HPLC analyses were performed at a wavelength of 280 nm using a Waters 6000 A solvent delivery system (Waters Associates, Etten-Leur, The Netherlands), a Uvikon 740 LC spectrometer (Kontron, Zurich, Switzerland), and a µBondapak C18 reversed-phase column (150× 19 mm). The mobile phase consisted of methanol : water (40 : 60, v/v), and elutions were carried out at a flow rate of 1 ml/min. Radioactivity was determined by liquid scintillation counting of fractions following HPLC. The liquor etoposide concentration was quantitated by comparison of the ratio of the peak height of the sample to that of specimens containing known etoposide concentrations, corrected for recovery in relation to the internal standards.

Results

In the patient 1, CSF levels taken at 2–2.30 h after the administration of 0.5 mg etoposide ranged from 3.6 to 5.2 µg/ml (n = 4 determinations). CSF levels taken at 22–24 h after etoposide administration ranged from 0.2 to 0.6 µg/ml (n = 8 determinations). In patient 2, CSF levels taken at 1, 2, 3 (n = 2 determinations), 8, and 16 h after the administration of 0.5 mg etoposide were 4.7, 2.0, 1.1, 0.8, 0.2, and 0.8 µg/ml, respectively. The elimination curve calculated for etoposide in CSF in patient 2 is shown in Fig. 1.

Discussion

Etoposide is a lipophilic drug that exhibits moderate penetration into the CSF. The lower than expected concentrations in CSF are usually explained by the high protein binding of etoposide in serum [3]. Using i.v. administration of high doses of etoposide (0.9–2.5 g/m^2), CSF levels of up to 0.54 µg/ml have been obtained [5]. Following i.v. high-dose etoposide monotherapy and treatment with etoposide-containing combination chemotherapy regimens, antitumor activity against cerebral metastases of SCLC has been observed [4–6]. Thus, the administration of high-dose etoposide could represent a useful approach to the management of SCLC patients presenting with CNS metastases. However, high-dose etoposide has been associated with severe toxicity, which prohibits its extensive use [7]. Therefore, intraventricular therapy remains the first choice for the treatment of patients exhibiting neoplastic meningitis.

Thus far, little experience has been obtained with the intraventricular treatment of SCLC using etoposide. Methotrexate is the agent most commonly used in the treatment of neoplastic meningitis. For patients presenting with meningeal carcinomatosis from SCLC, intraventricular treatment with etoposide seems to be more appropriate than therapy with methotrexate because etoposide is one of the most active agents against this disease. Moreover, in patients relapsing with meningeal leukemia, there is a need for more active agents that can be used intrathecally, since most of these individuals have previously received intrathecal methotrexate.

In the two cases described herein, 0.5 mg i.v. etoposide formulation could be given intrathecally once or twice daily without producing any side effects. However, in escalating the dose of etoposide, care must be taken when the i.v. formulation is used, since this formulation contains organic solvents that can theoretically cause adverse events. CSF levels measured at approx. 2 h after the administration of etoposide ranged from 2.0 to 5.1 µg/ml, which is considerably higher than those found after the i.v. administration of high-dose etoposide [5].

Our limited pharmacokinetic data, indicated that the estimated initial half-life ($t_{1/2\alpha}$) of etoposide in CSF was 1 h in patient 2. This low $t_{1/2\alpha}$ value may be explained by the low protein binding of etoposide in CSF. In fact, the CSF protein concentration in the patient 1 was <200 mg/l. Since etoposide is a lipophilic drug, it may be rapidly

cleared from the CSF. There was no sign of drug accumulation in the CSF when 0.5 mg etoposide was given twice daily. In view of the rapid clearance of etoposide from the CSF and the observation that the drug most probably becomes cytotoxic when levels are continuously maintained at >1 μg/ml, repetitive administration of doses of 0.5 mg twice daily seems to be preferable.

In conclusion, these preliminary results suggest that low doses of etoposide can be given intraventricularly without producing toxicity and that such therapy may be effective in the treatment of neoplastic meningitis. Therefore, further investigation of this new approach is warranted.

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