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Short communication

Complete remission of brain metastases of ovarian cancer following high-dose carboplatin: a case report and pharmacokinetic study

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Summary. Brain metastases developed in a 40-year-old woman with relapsed ovarian cancer 2 years after cisplatin-based combination chemotherapy. After a single dose of 800 mg/m^2 carboplatin, complete remission of the brain metastases occurred. A pharmacokinetic study during the second course revealed low levels of carboplatin in the cerebrospinal fluid.

Introduction

Brain metastases of epithelial ovarian carcinoma are rare, occurring in only about 2% of patients at a mean interval of approximately 2 years after the initial diagnosis [3, 7]. The incidence of brain involvement appears to be increasing, possibly as a result of the prolonged survival of patients with advanced ovarian cancer who are treated with cisplatin-containing combination chemotherapy [2, 11].

In general, brain metastases are treated with corticosteroids and/or radiotherapy, as the central nervous system (CNS) is generally considered to be a pharmacologic santuary for most systemically delivered chemotherapeutic agents [3, 5]. We observed a patient with brain metastases of ovarian cancer who achieved a complete remission of the brain metastases within 4 weeks after a single i.v. administration of high-dose carboplatin.

Case report

In 1985 a stage III serous papillary adenocarcinoma of the ovary was diagnosed in a 40-year-old woman. After cytoreductive surgery, six courses of chemotherapy consisting of cyclophosphamide, Adriamycin and cisplatin (CDDP) were given. A second-look laparotomy revealed minimal residual disease, and three further courses of CDDP were given. Two years later, mental changes and ataxia were observed and, subsequently, multiple cerebral and cerebellar metastases with signs of hydrocephalus were demonstrated on a computerized tomographic (CT) scan of the brain. A ventriculo-atrial drain was inserted; the mental changes improved but the ataxia persisted. A further non-invasive evaluation revealed a single liver metastasis. The serum CA-125 level was 3,745 units/l (normal, <30 units/l). Carboplatin (800 mg/m^2) was given as a 2-h infusion. The neurological features subsided over the subsequent weeks and a repeat CT of the brain carried out 4 weeks later showed complete remission of all metastases. Three consecutive monthly courses of single-agent car-

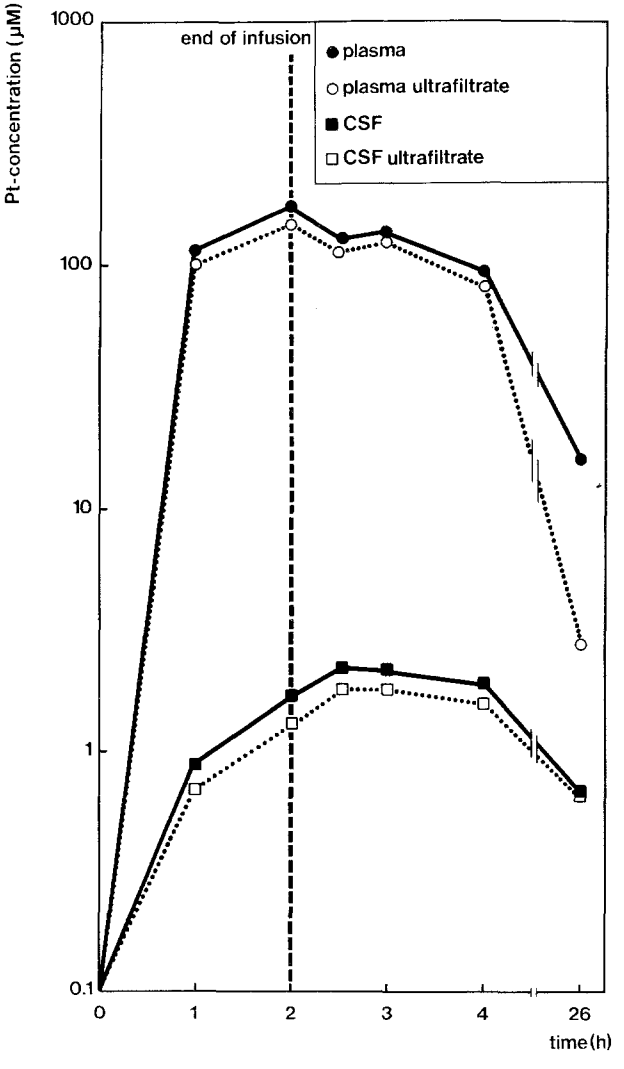

Fig. 1. Pharmacokinetic study during the second course of 800 mg/m^2 carboplatin, when the brain metastases were in complete remission

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boplatin were delivered. Because of severe thrombocytopenia, the dose of carboplatin was reduced to 600 mg/m^2 and 400 mg/m^2 in the third and fourth courses, respectively. The CT scan of the brain remained normal until 4 weeks after the last course, when a relapse of the cerebellar metastases was demonstrated. The liver metastasis continued to decrease in size. The CA-125 level had decreased to 75 units/l.

Pharmacokinetic study

Sampling of plasma and cerebrospinal fluid (CSF) took place following the second course of 800 mg/m^2 carboplatin, when the patient was known to have achieved complete remission of the CNS metastases. CSF was obtained from the ventriculo-atrial drain. The plasma and CSF were stored at −18° C until use. Total and ultrafiltrate platinum concentrations were determined by flameless atomic absorption spectroscopy (AAS) as previously described [8]. The results of the pharmacokinetic study are shown in Fig. 1. The peak concentrations of platinum in plasma and CSF were 176 and 2.2 μ*M*, respectively. During the first 4 h after infusion, the CSF/plasma ratios never exceeded 0.02. After 26 h, when the CSF concentration was approximately 0.8 μ*M*, the CSF/plasma ultrafiltrate ratio was 0.25. The pharmacokinetic study could not be extended beyond 26 h; thus the possibility of prolonged CSF levels on this order of magnitude cannot be excluded.

Discussion

The dramatic response of the brain metastases in our patient demonstrates that active tissue concentrations can be achieved in CNS metastases after a single dose of 800 mg/m^2 carboplatin. Because of its relatively high molecular weight and poor lipid solubility, carboplatin is expected to penetrate the blood-brain barrier poorly [5, 6]. However, the integrity of the blood-brain barrier in CNS tumors has been questioned, since morphological alterations in the microvascularity of brain tumors have been reported [5]. In that case, drug delivery to these tumors should not be impeded. Recently, objective responses following systemic treatment with 560 mg/m^2 carboplatin have been observed in children with primary CNS tumors [4].

The CSF levels and CSF/plasma ratio of carboplatin measured during the second course, when the brain metastases were in complete remission, were low. It is conceivable that during the first course, the blood-brain barrier had been disrupted in the metastatic brain tissue, such that cytotoxic concentrations in brain metastases could be achieved [5]. In addition, it should also be noted that the CSF levels measured do not correlate well with the concentration in brain tissue. Significant concentrations of carboplatin can be experimentally achieved for at least 10 days in normal mouse brain tissue after a single maximum tolerated dose of 60–80 mg/kg [1, 10].

High-dose carboplatin can induce objective responses in approximately 50% of patients with ovarian cancer refractory to conventional cisplatin-based chemotherapeutic regimens [9, 12]. This case report shows that a good response in brain metastases can also be obtained with such a regimen.

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