computed tomography (CCT) was normal. Since several hepatic metastases of the colon carcinoma were diagnosed at the same time, the neurological symptoms were considered to be possibly due to a paraneoplastic syndrome and therapy with FA/5-FU was started in September 1992.

At the end of the 5-FU infusion the patient developed various neurological symptoms with seizures, psychomotor epilepsy and local and temporal disorientation for several hours. She recovered completely within 24 h. EEG and CT were unchanged compared with findings in June 1992. Meanwhile, under phenytoin medication two further infusions of FA/5-FU have been given without any complications.

The third patient, a 64-year-old previously healthy male patient with inoperable hepatocellular carcinoma, received four infusions of FA/5-FU without any side effects. Three days after the fifth infusion, serious adverse effects occurred with diarrhoea grade 3, nausea grade 3, mucositis grade 2 and leukopenia grade 3. The patient was hospitalised for dehydration but in spite of parenteral hydration his clinical condition worsened. Six days after the last infusion of chemotherapy he developed a general seizure of grand mal type lasting for several minutes. Neurological examination some hours later was unremarkable as was the CT scan. In the following days stupor and coma developed without impairment of hepatic function and the patient died 17 days after the last chemotherapy. Autopsy was not performed.

The last patient, a 56-year-old female, received chemotherapy with FA/5-FU for carcinoma of the bile ducts with hepatic metastases. Twelve hours after the first 5-FU infusion the patient developed a severe headache. A transient blood pressure of 95/70 mmHg was found. Within hours a stroke-like picture developed with a left sided hemiplegia. CT scan and analysis of cerebrospinal fluid were unremarkable, but EEG revealed considerable right-sided disturbances.

The patient's clinical condition rapidly worsened and she expired 48 h after the end of the 5-FU infusion. Cerebral autopsy was completely unremarkable yielding no explanation for the clinical picture.

Neurotoxicity is a well known, but rather rare adverse effect of 5-FU [2, 3]. In the older literature the incidence ranges from 0.9 to 7% [2, 3]. It has been observed after 5-FU alone or in combination with allopurinol, folinic acid, thymidine and PALA [4–8]. The main symptoms are acute cerebellar ataxia, lethargy and seizures. Apparently, the only suspected risk factor for the occurence of neurotoxicity is the 5-FU dose intensity. The incidence of neurotoxicity seems to increase with higher 5-FU doses [2, 9]. Our findings with weekly FA/high-dose 5-FU also supports this assumption. The fact that in 2 of 3 patients with seizures after 5-FU previous neurological disturbances were known suggests that this fact may be—besides high-dose 5-FU intensity—another risk factor for this complication. Our finding that cytostatic therapy could be safely continued in patients with seizures when prophylactic anticonvulsant medication was used could be clinically important. Only the communication of other cases of neurotoxicity following this type of treatment may reveal the true incidence of this serious complication.

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EAP in Advanced Gastric Cancer

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THE REPORT by Preusser *et al.* [1] stimulated interest in the treatment of advanced gastric cancer with a new chemotherapeutic regimen composed of etoposide, doxorubicin and cisplatin (EAP) [1].

Response rates ranging from 48 to 72% were reported by some authors [2–4] although these were associated with substantial toxicity. At lower toxicity levels, lower response rates of 0–15% were reported [4–7].

From January 1990 to December 1991 we treated 20 previously untreated advanced gastric cancer patients with EAP.

The patients were less than 70 years of age, were considered to have a life expectancy of >3 months and had histologically confirmed gastric cancer. There were 13 males and 7 females with a median age of 55 years (range 23–67).

6 patients had non-resectable disease and 14 had disease extension following surgery.

All patients received at least two cycles of treatment, with a maximum of six cycles in the case of response or stable disease.

2 patients (10%) obtained complete response (CR) and 1 (5%) partial response (PR) with a respective duration of 7, 6 and 7 months.

Severe toxicity resulted in 1 case of disseminated intravascular coagulation (DIC) (rapidly resolved), 3 cases of leuco-thrombocytopenia, 1 case of diarrhoea, 8 cases of nausea/vomiting and

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11 cases of alopecia. Some patients presented lower grade cardiovascular, hepatic, renal and gastrointestinal toxicity. Mild alopecia, nausea and vomiting and leucopenia were observed in all remaining patients.

In common with the experience of Kelsen *et al.* [8] and Lerner *et al.* [9], who compared EAP versus FEM-TX in a phase II study, our results suggest a poor impact as regards the benefits/toxicity ratio.

When Sparano and Wiernik (1990) and Taal *et al.* (1990) published their data [5, 6] and criticised the results of Preusser, the latter suggested that the exact dosage of drugs had probably not been administered and that an accurate selection of patients with good performance status was needed [10].

Our experience, even with a correct schedule of drugs, confirms the limited efficacy of this regimen.

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Fatal Cerebrovascular Accident Associated with Chemotherapy for Testicular Cancer

Arthur Gerl, Christoph Clemm, Michael Schleuning and Wolfgang Wilmanns

A 42-YEAR-OLD MAN underwent orchidectomy for an embryonal cell carcinoma of his left testicle. Retroperitoneal lymphadenectomy revealed no nodal involvement. The patient was normotensive. He smoked cigarettes but he had no other risk factors for arteriosclerosis. Moreover, he had no history of vascular disease, coagulopathy or endocarditis. Two months after surgery two pulmonary nodules were detected by computed tomography (CT) scan but there were no other signs of relapse. Serum tumour markers human chorionic gonadotropin and alpha-fetoprotein were not elevated at any time. Chemotherapy was administered consisting of cisplatin 20 mg/m^2 for 5 days, etoposide 100 mg/m^2 for 5 days, and bleomycin 30 mg on days 1, 8 and 15. The first cycle was uneventful but 2 days after the second course the patient became stuporous and developed global aphasia and right hemiparesis. On an immediate CT scan no abnormalities were identified. However, a second CT scan 6 h after the onset of symptoms disclosed an oedema of the left cerebral hemisphere. Angiography revealed an occlusion of the left middle cerebral artery. Local fibrinolysis with tissue plasminogen activator was performed. The thrombus resolved but the patient's neurological deficits deteriorated. He died from uncontrollable cerebral oedema 34 h after the onset of neurological symptoms. On postmortem examination pulmonary lesions or metastatic spread to any other site were not detectable. There was also no evidence of cerebral tumour embolism. Examination of the brain showed an extended softening region in the left hemisphere. Microscopically, no tumorous infiltration was identified.

Cerebrovascular complications following cisplatin-based chemotherapy of germ cell tumours have been reported infrequently [1–4]. A close temporal association between the administration of chemotherapy and the vascular event in the majority of cases suggests a causal relationship. Moreover, the young age of patients and the lack of vascular risk factors in most of the reported cases argue against coincidence. As tumour embolisation was not found in our case and was deemed improbable in previous reports [1, 2, 4], cerebrovascular accidents presumably are caused by toxic side-effects of antineoplastic agents. Platelet activation, an alteration of the clotting system and a disturbance of prostacyclin-thromboxane homeostasis may be pathogenetic factors [5]. An alteration of vascular smooth muscle tone due to cisplatin-induced renal magnesium wasting is a further possible mechanism. Recently, the endothelium of tumour vessels was recognised as a potential target of antineoplastic treatment [6, 7]. As the vascular toxic effect may be not strictly confined to the more rapidly proliferating endothelial cells in tumour tissue, an injury of normal vessels may occur which might usually be subclinical. However, in a small subset of patients vascular lesions apparently lead to acute ischaemic events. A cumulative vascular damage due to the administration of sequential chemotherapy cycles may play a role, since in the majority of reported cases patients had received more than one cycle prior to the vascular event [1, 2, 4].

Although cerebrovascular complications following cisplatin-based chemotherapy of germ cell tumours seem to occur infrequently, they are of especial clinical interest, as they arise in young patients who have a high chance of cure. Moreover, these complications may be fatal as in the case presented here and in a previously described case [4].

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