Reversible posterior leukoencephalopathy after combination chemotherapy

Abstract  We describe a young woman with Burkitt’s lymphoma, treated with intravenous adriamycin and cyclophosphamide and intrathecal cytarabine. She developed a reversible posterior leukoencephalopathy syndrome (RPLS) with typical MRI findings. Diffusion-weighted images during the first days after the onset of symptoms predicted a small irreversible lesion in the frontal lobe, verified on T2-weighted images 1 month later. The patient showed full recovery after high-dose steroid treatment.

Key words  Chemotherapy · Cytarabine · Cyclophosphamide · Adriamycin · Leukoencephalopathy · Magnetic resonance imaging

Introduction  Neurotoxicity is a well-recognised and relatively common property of cytostatic drugs. In the central nervous system various forms of encephalopathy may result from chemotherapy, and in the peripheral nervous system neuropathy is the usual side-effect of antineoplastic agents. The neurotoxic effects can be classified into acute, subacute or early-delayed and chronic or late-delayed. Acute and subacute reactions are usually reversible, whereas the chronic changes are usually irreversible [1]. Acute encephalopathy induced by chemotherapy may be fatal [2, 3] but, in general, acute reactions are mild and do not require specific treatment. However, severe acute reactions to chemotherapy include seizures, loss of consciousness and disturbed vital
functions, requiring intensive care. Recognition of the acute reaction as a neurotoxic side-effect of the cytostatics used is important, since these side-effects require discontinuation of the chemotherapy [1].

Case report

A 17-year-old woman with recently diagnosed stage IV Burkitt’s lymphoma was treated according to the MACOP-B protocol: she received 2.1 g cyclophosphamide with mesna intravenously for 1 day, with 250 mg methylprednisolone for 3 days. The cytostatic treatment was followed by extensive tumour lysis, requiring dialysis. After recovery from the renal failure, the patient received a second treatment consisting of 650 mg cyclophosphamide and 95 mg adriamycin with 75 mg/day oral prednisolone. Although no signs of cerebral lymphoma were observed, she received two doses of 55 mg intrathecal cytarabine prophylactically, according to the protocol. The first caused extensive headache, thought to be caused by meningeal irritation by cytarabine, and the second was given after 3 day interval, with 40 mg intravenous dexamethasone. Five days after the first intrathecal cytostatic the patient had her first tonic-clonic seizure.

On admission she was vomiting and her blood pressure was 152/104 mmHg. The following day she had several seizures and became lethargic. The seizures were first treated with intravenous diazepam and lorazepam, without significant response, and finally with intravenous phenytoin and midazolam. The electroencephalogram showed diffuse slowing and periodic sharp waves in the left occipital lobe. Frequent generalised discharges associated with convulsions were also seen. After the midazolam-phenytoin infusions the seizures ceased.

No abnormality was seen on cranial CT, but MRI revealed widespread high signal changes on T2-weighted fluid-attenuated inversion-recovery (FLAIR) images (Fig. 1). The lesions were primarily at the corticomedullary junction of the occipital, parietal and temporal lobes. There were also bilateral lesions in the cerebellar white matter. The largest lesion was in the left occipital lobe, corresponding to the focus seen on the EEG. Bilateral high-signal frontal foci were seen on diffusion-weighted imaging (DWI) (Fig. 2).

The patient was treated with 1 g methylprednisolone for 3 consecutive days. Twelve hours after the first dose, she regained consciousness. MRI 4 days later showed significant resolution of the lesions (Fig. 1); the cerebellar lesions had disappeared. The intensity of the high-signal right frontal focus on DWI had decreased, close to background, whereas the lesion in the left hemisphere was still visible (Fig. 2). The intravenous steroid treatment was followed by oral methylprednisolone (80 mg/day). Intrathecal cytarabine was thought to be the major factor triggering the acute encephalopathy, and treatment was continued with intravenous cyclophosphamide, dexamethasone and adriamycin. No intrathecal cytostatics were given and no complications developed after the third round of chemotherapy. MRI more than a month after the seizures showed almost complete resolution of the lesions (Fig. 1). A single minor high-signal lesion was still visible in the left frontal lobe, corresponding to the high-signal region on the first two DWI (Fig. 2).

Discussion

Cytostatic drugs exert their effects by limiting the growth of highly mitotic tumour cells, and it is understandable that the side-effects of chemotherapy affect other tissues containing rapidly dividing cells, such as bone marrow and the gastrointestinal tract. However, although the nervous system contains postmitotic or slowly dividing cells it is unexpectedly sensitive to chemotherapy. In the central nervous system, various types of encephalopathy or myelopathy can be caused by antineoplastic agents [1]. Although some cytostatic drugs cause typical lesions in the brain, such as cerebellar dysfunction associated with cytarabine, in general the encephalopathy caused by the various cytostatic drugs does not differ between the different agents. The risk of neurotoxic side-effects is increased if the drugs are given intrathecally or if chemotherapy is combined with cranial radiation [1].

Our patient had stage IV Burkitt’s lymphoma with large intra-abdominal masses. This aggressive lymphoma needs very intensive chemotherapy, with prophylactic intrathecal treatment, due to the high relapse risk, in the form of neurolymphoma [5]. Our patient first received intravenous cyclophosphamide alone followed by intravenous cyclophosphamide and adriamycin with intrathecal cytarabine. Intravenous cyclophosphamide appears to have little or no neurotoxic side-effects [1], although when it is combined with adriamycin, vincristine and prednisone a fatal, progressive leukoencephalopathy has been reported [3]. A single report describes leukoencephalopathy induced by cyclophosphamide and steroids [6]. There are no reports of leukoencephalopathy caused by systemic adriamycin alone. However, in combination with cyclophosphamide [7] or cyclophosphamide, vincristin and prednisone [3], adriamycin may induce a fatal encephalopathy. Intrathecal cytarabine has known neurotoxic properties, but the best characterised neurotoxic side-effect of intrathecal cytarabine is myelopathy, including the locked-in syndrome [1, 8]. As with cyclophosphamide and adriamycin, intrathecal cytarabine has been reported to cause acute encephalopathy in combination with other cytostatic drugs and/or cranial radiation [9–11], and a single report describes acute encephalopathy caused by intrathecal cytarabine alone [12]. It is difficult to judge which of the cytostatics used in our patient triggered the leukoencephalopathy. Since the first dose of intravenous cyclophosphamide did not have adverse effects, cyclophosphamide alone appears not to be a major factor. It is possible that the combination of cyclophosphamide and adriamycin was the major causative agent, but this seems unlikely, since intravenous cyclophosphamide and adriamycin did not induce the leukoencephalopathy again when given after the incident. Intrathecal cytarabine therefore, appears to be the major factor, especially since intrathecal cytostatics are likely to elicit encephalopathy more easily than those given systemically.

CT scan may reveal chemotherapy-induced lesions in the acute phase as low density supratentorial foci [2]. MRI is more sensitive and is the modality of choice...