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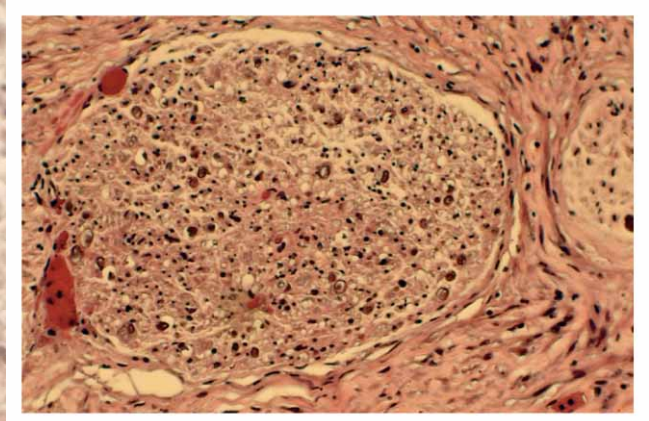
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Central Nervous System Toxicity of Chemotherapy

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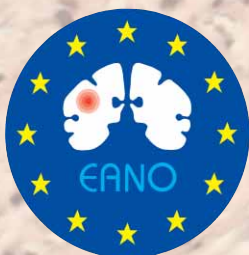
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Central Nervous System Toxicity of Chemotherapy

Uwe Schlegel

Abstract: Cytostatic drugs may exert toxic effects on the central nervous system by various mechanisms and may lead to reversible or irreversible neurologic dysfunction. The clinical symptoms are often self-limiting, but may be acute,

dramatic, and sometimes even fatal. Since causative therapeutic and even preventive measures are limited, the knowledge of risk factors, characteristic clinical symptoms, symptomatic treatment, and monitoring of the affected pa-

tients is essential. **Eur Assoc Neurooncol Mag 2011; 1 (1): 25–9.**

Key words: chemotherapy, neurotoxicity, central nervous system, prevention, therapy

■ Introduction

Several cytostatic drugs may harm the central nervous system after systemic (intravenous, oral) administration or after topical, ie intrathecal, intraventricular, or intraarterial application. The brain is at particular risk and side effects may present as acute, subacute, or chronic encephalopathy. Seizures, focal symptoms like aphasia or hemiparesis, and cortical blindness may occur as isolated symptoms. These symptoms may present immediately after chemotherapy administration or with delay. Aseptic meningitis is a typical complication of intrathecal therapy; particular drugs can cause cerebellar ataxia, often after a certain cumulative dose has been exceeded. Toxicity to the spinal cord is rare but severe and most frequently it is the result of intrathecal drug administration. Certain antibodies used in oncology, such as rituximab, are associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic infection with the JC virus as a result of immunosuppression. However, these and other “indirect” CNS complications of chemotherapy will not be addressed here.

Neurotoxic complications of chemotherapy frequently present with characteristic symptoms and need to be separated from other morphologic (ie metastatic), infectious, or metabolic causes of CNS dysfunction in oncology. Complete or partial recovery may frequently be encountered, but irreversible damage and even death are possible as well. Since therapeutic measures are often limited, prevention is necessary and requires knowledge of neurotoxic side effects to ensure careful monitoring of patients at risk. Discontinuation of chemotherapy is often the only method to prevent further CNS toxicity. The frequency of CNS toxicity depends on the drug chosen, on its single and cumulative doses, on the duration of treatment, and on additional risk factors, such as coexisting neurological morbidity. Well-known factors to substantially increase this risk are dose escalation, combination versus monotherapy, high-dose chemotherapy with stem cell transplantation, and irradiation (RT) of the brain, with chemotherapy after RT probably being more harmful than the reverse sequence [1, 2]. Cytostatics most frequently associated

with CNS toxicity are methotrexate (MTX), cytarabine (Ara-C), and ifosfamide. Table 1 shows chemotherapy-induced neurotoxic complications and the respective causative agents.

In the following, characteristic clinical pictures and cytostatics with well-known CNS toxicity will be described. Hypotheses with regard to pathogenesis and possible methods of prevention as well as therapy are discussed.

■ Acute Encephalopathy

Acute encephalopathy develops within a few hours to days after chemotherapy and presents with disorientation, confusion, agitation, and eventually coma. Myoclonic jerks, seizures, and hallucinatory symptoms may occur. The disorder has to be separated from non-convulsive epileptic state, (viral) encephalitis, metabolic disorders, paraneoplastic syndrome, such as limbic encephalitis, and others [2]. Protocols typically associated with acute encephalopathy include methotrexate (MTX), ifosfamide, and rarely others [3, 4] (Table 1).

Methotrexate

Acute encephalopathy is frequently self-limiting, but may be dramatic or even fatal: a life-threatening acute encephalopathy in a 32-year-old female came to our attention, who was treated for Burkitt lymphoma with 1.5 g/m² MTX intravenously (iv) over 24 hours and 15 mg intrathecally. She was found to be of homozygous allelic state of the G-allele of 5-methyltetrahydrofolate-homocysteine S-methyltransferase (MTR) c.2756A>G, which is observed in only approximately 4 % of the general population [5]. MTX-induced leukoencephalopathy and demyelination have been linked to functional polymorphisms in enzymes influencing the methionine-homocysteine pathway so that S-adenosylmethionine (SAM), the only methyl-group donor in the CNS, is reduced [6, 7] and levels of (toxic) homocysteine [8, 9] may be increased. MTX therapy leads to a lack of the folate derivate used as MTR co-factor and thus to reduced MTR activity resulting in a reduction of SAM bioavailability. The G-allele of MTR c.2756A>G may therefore have pronounced the adverse effect of MTX on SAM synthesis and this rare homozygous allelic state might have contributed to the acute MTX-induced encephalopathy in the patient observed [5]. Since oral SAM substitution can revert CNS demyelination in patients with (inborn) SAM deficiency, SAM and folate-derivates may be interesting candidates for treatment of MTX-induced neurotoxicity [5].

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Table 1. Clinical syndromes of CNS toxicity caused by cytostatic drugs

Acute (reversible) encephalopathy	Methotrexate (MTX) Ifosfamide Paclitaxel 5-fluorouracil (5-FU) Cytosine arabinoside (Ara-C) Procarbazine Nitrosoureas (high dose) Interferon- α Interleukin-2 Tamoxifen (high dose) Etoposide, VP16 (high dose) Steroids High dose with stem cell transplantation
Subacute encephalopathy	MTX Cis-platinum
Chronic encephalopathy	MTX iv/intrathecaly Infrequently others High-dose polychemotherapies
Reversible posterior (leuko-) encephalopathy syndrome (PRES)	Cyclosporine Combination therapy including cyclophosphamide, Ara-C, cis-platinum, cyclophosphamide, ifosfamide, vincristine, gemcitabine, other immunosuppressants
Multifocal leukoencephalopathy	Capecitabine
Thrombotic microangiopathy	Mitomycin-C Gemcitabine Cyclosporine
Cerebral infarctions	MTX Cyclosporine Platinum derivatives
Cortical blindness	Platinum derivatives Fludarabine (high dose)
Cerebellar dysfunction	Ara-C 5-FU Infrequently vincristine, cyclosporine
Seizures	MTX, etoposide, VP-16 (high dose) Cis-platinum, vincristine, asparaginase BCNU, dacarbazine, amsacrin Busulfan (high dose), cyclosporine, misonidazole, paclitaxel
Aseptic meningitis	MTX, Ara-C (intrathecaly)

Ifosfamide

Ifosfamide is another drug known to potentially induce acute encephalopathy, which may be severe and may even cause death: in 10–15 % of patients treated with dosages > 1 g/m² disorientation, lethargia, and coma may occur [4]. Non-convulsive epileptic states caused by ifosfamide have been reported [10]. The pathogenesis is not fully understood, however, ifosfamide and its metabolites may interfere with thiamine function and with that of its phosphorylated forms TPP and TTP, while vitamin B₁ levels themselves are not decreased. Thus, prophylaxis with thiamine, 100 mg iv every 4–6 hours, has been proposed for prevention of ifosfamide-induced encephalopathy [11, 12] as has been therapy/prevention with methylene-blue 50 mg 6× per day iv [13]. However, the therapeutic value of these measures was not confirmed by a recent retrospective analysis [14] and remains difficult to interpret since spontaneous recovery is frequent. A risk factor associated with the occurrence of ifosfamide-induced acute encephalopathy is reduced serum albumine [4, 15].

■ Subacute Encephalopathy

Subacute encephalopathy is rare and may develop days to weeks after administration of MTX (iv or intrathecaly) or of cis-platinum, presenting as abrupt onset of confusion, seizures, focal signs, and symptoms such as hemiparesis and aphasia [4, 8, 16, 17]. Children are mainly affected [8, 16], but single cases in adults have been reported as well [17]. The mechanism of neurotoxicity is poorly understood: symmetrical hyperintense signals in diffusion-weighted imaging (DWI) and decreased apparent diffusion coefficient (ADC) on magnetic resonance imaging (MRI) paralleled the clinical symptoms in a patient reported and disappeared with their resolution. In the absence of vascular or perfusion changes, these MRI findings have been interpreted as cytotoxic oedema of the white matter but sparing the cerebral cortex [17]. Symptoms may resolve completely, however, lethal outcome has been observed [18]. In children suffering from subacute MTX-induced encephalopathy, dextrometorphan 1–2 mg/kg orally, a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, has been applied to 5 affected children, followed by complete resolution of symptoms [8], but has never been re-evaluated systematically since.

■ Chronic Encephalopathy

Chronic encephalopathy usually starts to develop with a latency of several months to years, is most frequently irreversible and sometimes even progressive. MTX-induced chronic encephalopathy is best known, however, other drugs or polychemotherapies such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) may also cause this complication, however, less frequently [1]. The main risk factor for the development of MTX-induced chronic encephalopathy is whole-brain irradiation [19]. The clinical spectra of chronic encephalopathy range from subtle memory disturbances, disorientation, lack of initiative and apathia to full-blown dementia. No efficient treatment is known. Cerebral imaging shows (often confluent) white matter disease, ie leukoencephalopathy, and progressive deep brain atrophy (Figure 1). It is of note, however, that even long-lasting extensive MTX-induced confluent white matter changes may be clinically asymptomatic [20]. High-dose chemotherapy with haematopoietic stem-cell support in patients with breast cancer was reportedly followed by memory disturbances in some of them [21], however, neuropsychometric findings from long-term follow-up are not available.

■ Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is clinically characterised by headache, visual disturbances, such as visual field deficits and cortical blindness, confusion, seizures, and eventually coma [1]. It has been associated with severe hypertension, eclampsia, but also with administration of immunosuppressants, antibodies, and other substances. In several instances, PRES has been reported after chemotherapy with [22] or without accompanying electrolytic imbalance [23]: T2-weighted MRI shows characteristic hyperintense lesions parieto-occipally involving the gray and white matters. These signal abnormalities are transient as

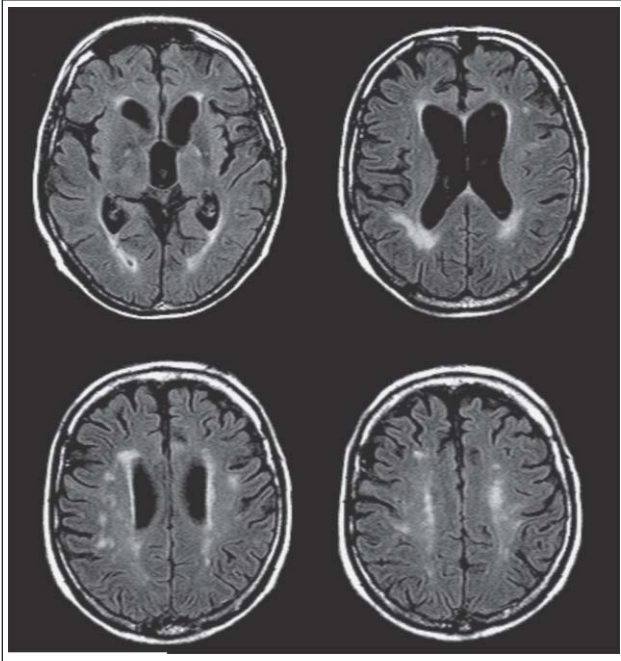


Figure 1. Cerebral MRI (FLAIR) of a 35-year-old male, treated with MTX-based chemotherapy and whole-brain irradiation at the age of 20: ongoing complete response of a high-grade malignant Non-Hodgkin's B-cell lymphoma. Cognitive dysfunction due to leukoencephalopathy and deep-brain atrophy.

is the clinical syndrome, which usually resolves within days after cessation of therapy and symptomatic treatment of seizures and electrolytic imbalance [22].

■ Cerebellar Dysfunction

Cerebellar dysfunction with dysarthria, nystagmus, and ataxia is a typical complication of cytarabine, usually at cumulative dosages $> 36 \text{ g/m}^2$ [4], however, this complication has been encountered in single cases with lower dosages. Neuropathologic examination of patients coming to die with but not because of this complication showed widespread Purkinje cell loss [1]. Risk factors for the development of cerebellar dysfunction are older age, increased serum creatinine, and alkaline phosphatase [24]. The disorder is rarely accompanied by an acute encephalopathy, which is reversible after cessation of therapy. A similar cerebellar syndrome may be encountered after therapy with high-dose 5-fluorouracil, which is reversible after interruption of therapy, but may recur at drug re-exposure [1].

■ Cerebral Infarctions

Single cases of cerebral ischemia after MTX, platinum-derivates, and cyclosporine have been reported, primarily in children treated with MTX for acute leukaemia [16]. Patients receiving high doses may develop microangiopathy with calcifications in the vessel wall [16]. Thrombotic microangiopathy has been reported after exposure to mitomycin C, gemcitabine, and cyclosporine [1].

■ Myelopathy

Acute myelopathy with ascending para- or tetraparesis is a rare but devastating complication of intrathecal therapy with

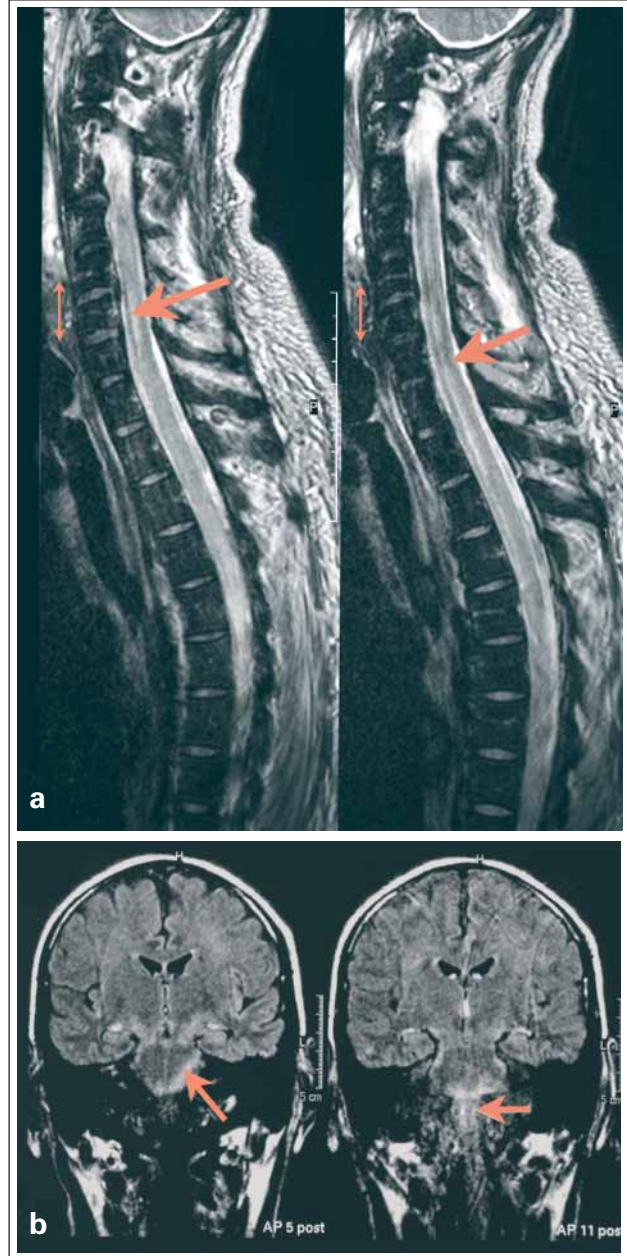


Figure 2. (a) MRI (T2-weighted) of the cervicothoracic spine showing extensive myelopathy (arrows) after intrathecal MTX 12 mg, Ara-C 30 mg + prednisolone 2.5 mg in a 31-year-old male treated for leukaemia ("triple therapy"): tetraplegia developing over 24 hours shortly after application. (b) Cerebral MRI (FLAIR) showing affection of the pons (arrow) and medulla (arrow) resulting in coma and mechanic ventilation. Incomplete recovery with persistent paraparesis and severe bilateral hyakusis.

MTX [25], Ara-C [26] or with a combination of these („triple-therapy“ with MTX, Ara-C, and steroids) [1, 25–27]. It can occur even after single-dose exposure, may involve the brainstem, as exemplified in Figure 2, may lead to a locked-in syndrome [1] or even death due to acute “encephalomyelitis” [28]. Possible risk factors are extensive meningeal disease, irradiation of the CNS, and childhood or old age [2]. The pathologic finding is that of a necrotizing myelopathy; efficient therapies have not been established. However, a recent case has been reported on a 54-year-old female with MTX-induced severe myelopathy who showed partial remission of symptoms beginning 3 days after continuous substitution of S-adenosymethionine (SAM) $3 \times 200 \text{ mg/die}$, folic acid $4 \times$

Table 2. Therapy/prophylaxis of chemotherapy-induced CNS toxicity

Drug	Symptoms	Frequency	Threshold dosage	Risk factor	Therapy/prophylaxis
Methothrexate	Acute reversible encephalopathy	Rare	> 0.5 g/m ² (?)	Whole-brain radiotherapy	Frequently self-limiting
	Subacute encephalopathy	Very rare	After 2 nd or 3 rd iv application	Homocysteine ↑	Dextrometorphan (?)
	Chronic encephalopathy	Infrequent after MTX alone	> 0.5 g/m ² (?)	Whole-brain radiotherapy, intrathecal MTX	None
	Meningitis	< 10 %	Only after →	intrathecal application	Symptomatic
	Seizures	Infrequent	?	Seizures prior to application	Symptomatic
	Myelitis/myelopathy	Very rare	?	Young/old age, aggressive leukaemia, radiotherapy	"CSF exchange"? Multiple folate metabolites
Ara-C	Cerebellar dysfunction + facultative acute encephalopathy	Frequent, if →	cumulative dose > 36 g/m ²	Renal insufficiency, alkaline phosphatase ↑ age > 60, neurological comorbidity	Frequently self-limiting
	Meningitis	like →	MTX		
	Myelitis	like →	MTX		"CSF exchange"?
5-Fluorouracil	Acute encephalopathy	Rare	?	Dihydropyrimidine dehydrogenase ↓	None
	Cerebellar dysfunction + facultative additional CNS symptoms			+ Allopurinol + N-Phosphonoacetyl-L-aspartat (PALA) + thymidine	Often self-limiting
	Inflammatory multifocal leukoencephalopathy			+ Levamisol	None
Ifosfamide	Acute encephalopathy	Up to 30 %	?	High dose, renal, hepatic insufficiency, albumine ↓	Frequently self-limiting; methylene-blue, thiamine?

20 mg/die, cyanocobalamine 100 µg/die and methionine 5 g/die (iv for one week, then orally) [29]. For lack of other established treatments, substitution of these derivatives of the folic acid and methionine/homocysteine metabolic pathway may be tried as well as complete CSF "exchange".

■ Others

Other neurotoxic complications of chemotherapy are listed in table 2. Five patients with capecitabine-induced multifocal leukoencephalopathy have been described with clinically and radiologically (nearly) complete resolution of signs and symptoms after discontinuation of the drug [30]. Cortical blindness may occur as an isolated symptom after cis-platinum or fludarabine administration [1]. Seizures may follow the administration of many drugs, in particular the systemic or intrathecal application of MTX [31]. Aseptic meningitis and headache affect about 10 % of patients receiving intrathecal chemotherapy [2].

■ Differential Diagnosis

The diagnosis of chemotherapy-related neurotoxicity can only be established if other possible causes of neurologic dys-

function are excluded: Parenchymatous and/or leptomeningeal metastatic disease has to be ruled out by MRI and CSF analysis. Epileptic seizures may present as non-convulsive status epilepticus, which can only be diagnosed by EEG recording. This is in particular necessary if ifosfamide-induced acute encephalopathy is suspected, since ifosfamide may cause a non-convulsive status [10] which needs to be treated accordingly. Routine clinical chemistry including electrolytes and metabolic measures are essential since in patients treated for malignant tumours, infectious complications, electrolytic imbalances, disturbances of osmolarity, renal and hepatic failures, thiamine deficiency, endocrine disturbances, and tumour lysis syndrome need to be considered. The diagnosis of a paraneoplastic neurological syndrome can be confirmed by detection of specific antibodies.

■ Conflict of Interest

The author has received honoraria from Essex-Pharma, Mundipharma, Amgen, and Sigma-Tau.

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