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MINI REVIEW

Central and peripheral nervous system toxicity of common chemotherapeutic agents

Chrissa Sioka · Athanassios P. Kyritsis

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Abstract Central and peripheral nervous system toxicity are frequent complications of most chemotherapy regimens, often leading to reduction of dosages or cessation of the responsible drugs. However, sometimes the afflicted toxicity may not be reversible, especially if it is not recognized early, further compromising the quality of life of the cancer patients. The most common chemotherapeutic agents that might cause CNS toxicity manifested as encephalopathy of various severities include methotrexate, vincristine, ifosfamide, cyclosporine, fludarabine, cytarabine, 5-fluorouracil, cisplatin and the interferons (alpha > beta). Involvement of the peripheral nervous system manifested as distal peripheral neuropathy results after therapy with cisplatin, vincristine, taxanes, suramin and thalidomide. Although several compounds have been proposed as neuroprotective agents, few have been shown to be active against the chemotherapy induced neurotoxicity.

Keywords Neurotoxicity · Chemotherapy · Central nervous system · Brain · Cancer

C. Sioka · A. P. Kyritsis
Neurosurgical Research Institute,
University of Ioannina, 45110 Ioannina, Greece

C. Sioka
Department of Nuclear Medicine,
University Hospital of Ioannina, 45110 Ioannina, Greece

A. P. Kyritsis (✉)
Department of Neurology,
University of Ioannina School of Medicine,
University Campus, 45110 Ioannina, Greece
e-mail: thkyrits@uoi.gr

Introduction

The induction of peripheral neuropathy is a common limiting factor during chemotherapy of cancer. Little is known about the mechanisms responsible for the development of neuropathy. Depending on the substance used, a pure sensory and painful neuropathy (with cisplatin, carboplatin) or a mixed sensorimotor neuropathy with or without involvement of the autonomic nervous system (with vincristine, taxanes, suramin and other drugs) may occur [1]. Some chemotherapeutic drugs result in mental status changes due to acute hyperammonemia [2]. Both cisplatin and ifosfamide can cause acute or delayed central nervous system (CNS) toxicity. While ifosfamide neurotoxicity has been predominantly associated with neuropsychological impairment without evidence of structural abnormalities in neuroimaging studies, cisplatin has been shown to cause cerebrovascular complications. Various pathophysiologic conditions may contribute to these complications including thrombosis secondary to vascular endothelial injury or thromboembolic events [3]. Although the most neurotoxic effects of chemotherapy are at least partially reversible upon early recognition, severe irreversible damage may ensue if the condition is not recognized and the toxic drugs continue. This article will review the neurotoxicity induced by most common chemotherapeutic agents, and when available use of available neuroprotective agents.

Interferons

Development of neuropsychiatric symptoms, predominantly depression, is the reported side-effects associated with use of interferons (Table 1). For depression, the evidence of increased risk is stronger for interferon-alpha than

Table 1 CNS toxicity of common chemotherapeutic drugs

Drugs	Encephalopathy	Epileptic seizures	Cranial neuropathy
Interferons [4–7]	Interferon-alpha > Interferon-beta Frequently depression, reversible Rarely, cognitive dysfunction		
Methotrexate [8–13]	Asymptomatic white matter changes or symptomatic CNS demyelination (bilateral focal findings, cognitive dysfunction)	Yes	No
Vincristine [15, 16]	Bilateral white matter changes with focal findings	Yes	Yes (usually abducens nerve palsy)
Ifosfamide [17–19]	Bilateral white matter changes, focal findings, mental status changes, coma	Yes, sometimes non-convulsive status epilepticus	No
Cyclosporine/Tacrolimus [22–25]	Bilateral occipital lobe, brainstem and cerebellar changes Confusion, aphasia, parkinsonism, cortical blindness, coma	Yes	Yes
Fludarabine [26–29]	Diffuse necrotizing occipital encephalopathy Progressive multifocal leukoencephalopathy	Yes	No
Cytarabine (Ara-C) [30–33]	Acute cerebellar syndrome with ataxia Reversible occipital encephalopathy	Occasionally	Yes
5-Fluorouracil [34–36]	Reversible encephalopathy Sometimes, acute cerebellar syndrome with ataxia	Rarely	Rarely
Taxanes [42, 43]	Rare, after whole brain radiotherapy or brain surgery [44]	No	No
Cisplatin [49, 50]	Reversible occipital encephalopathy with blindness and mental status changes	Occasionally	Occasionally

for interferon-beta. The availability of preventive and treatment interventions suggest that neuropsychiatric toxicity can often be managed without needing to discontinue the treatment [4]. Although use of interferon-alpha treatment in oncological settings may be associated with depression [5], a recent study showed that most depressive episodes were self-limiting and were associated with either episodes of flu-like symptoms common at the start of the treatment or with concurrent psychosocial events [6]. However, other studies demonstrated that, in some cases, interferon neurotoxicity was not reversible and manifested with cognitive symptoms from mild to moderate in severity. In such cases, the neuropsychological test abnormalities were consistent with frontal-subcortical dysfunction [7].

Methotrexate

The antitumor effect of methotrexate is due to the inhibition of dihydrofolate reductase, which recycles oxidized folates to their reduced state. Polyglutamation of methotrexate leads to purine synthesis inhibition and prolongs the intracellular retention of the drug [8]. The typical side-effects of high-dose MTX chemotherapy on the CNS range from asymptomatic white matter changes to severe CNS demyelination (Table 1). MTX neurotoxicity has been described to be associated with homocysteine and folate levels as well as genetic variants affecting methionine metabolism. In a case of severe, acute MTX-induced encephalopathy, homozygosity for the rare missense variant methionine synthase c.2756A>G (D919G), which may has modified the effect of MTX on homocysteine metabolism, was described. This finding encourages further studies to determine to what extent the individual conditions of folate and methionine metabolism influence the effects or side-effects of MTX treatment [9].

Subacute MTX neurotoxicity is manifested by onset of focal cerebral dysfunction occurring days to weeks after MTX administration. Imaging may show bilateral symmetrical restricted diffusion involving white matter of the cerebral hemispheres, which may be reversible [10] after a few days of termination of therapy [11], and no perfusion abnormalities. The absence of vascular or perfusion abnormalities suggests that transient cytotoxic edema in white matter may explain the syndrome of subacute MTX neurotoxicity [12]. However, in some cases, vascular disease may be a component of this white matter injury [13]. Occasionally, reversal of methotrexate-induced leukoencephalopathy can be obtained with high-dose folinic acid (Table 3) [8].

Vincristine

Vincristine is a well-known neurotoxic chemotherapeutic agent. Dose dependent and cumulative peripheral neuropathy

is the main dose-limiting side-effect of chemotherapy with vincristine (Table 2). Paresthesias, loss of tendon reflexes, and progressive weakness are the most common clinical features, although sensory impairment, cranial nerve palsies, gastrointestinal disturbances, and autonomic dysfunctions including atonic bladder, impotence, and orthostatic hypotension might occur. In addition, vincristine treatment seems to exert a neurotoxic effect on the efferent olivocochlear system, which takes place early in the course of chemotherapy [14]. Neurotoxicity may be also manifested with seizures and bihemispheric lucencies on brain imaging studies, which can be reversible upon cessation of vincristine (Table 1) [15]. Isolated ocular muscle paresis, such as abducens nerve palsy, which can be the presenting sign of a toxic neuropathy associated with vincristine use [16].

Ifosfamide/cyclophosphamide

Cyclophosphamide and ifosfamide are alkylating agents and they are prodrugs that require activation by hepatic microsomal enzymes before being metabolized to their respective cytotoxic species, phosphoramide mustard and ifosfamide mustard. They alkylate DNA, forming DNA–DNA cross-links that result in inhibition of DNA synthesis and cell death. Leukopenia is the dose-limiting toxicity of cyclophosphamide, and neurotoxicity is the dose-limiting toxicity of ifosfamide when preventive measures are taken to reduce urotoxicity [17]. Ifosfamide is used in the treatment of germ-cell tumors, sarcomas and lymphomas. A total of 10–16% of patients treated with ifosfamide develops an encephalopathy, which may manifest itself as a variety of symptoms, ranging from agitation to seizures and coma (Table 1) [18]. Changes in mental status of patients following infusion of ifosfamide should also prompt the treating physician to rule out nonconvulsive status epilepticus [19]. The exact pathophysiologic mechanisms responsible for the development of ifosfamide-induced encephalopathy are not known. However, accumulation of chloracetaldehyde, toxic metabolite of ifosfamide, in the CNS is theorized to be the cause of the neurotoxicity. No standard treatment has been available for ifosfamide-induced encephalopathy. Recently, many reports suggested that methylene blue may be an effective treatment of this lethal complication (Table 3) [20]. Facing a clinical diagnosis of ifosfamide encephalopathy, it is recommended to discontinue administration of ifosfamide and inject by intravenous route 50 mg methylene blue every 4 h until the symptomatology recedes. The re-challenge of ifosfamide is not contraindicated and should be performed under prophylactic treatment with methylene blue by intravenous route at the dose of 50 mg every 6 h [21].

Cyclosporine/tacrolimus (FK-506)

Transplantation conditioning regimens have been shown to affect the brain imaging appearance in patients with

Table 2 Types of neuropathies associated with chemotherapy

Type of neuropathy	Chemotherapeutic agent	Differential diagnosis
Pure sensory	Cisplatin [45] Oxaliplatin [51–54]	Anti-Hu paraneoplastic syndrome
Mixed sensory-motor	Vincristine [14] 5-Fluorouracil (rare) [37] Taxanes [38] Thalidomide [55–58]	Diabetes mellitus Hypothyrodism B12/folate deficiency Collagen vascular disease Pre-existed hereditary neuropathy
Autonomic	Vincristine [14]	Other causes of atonic bladder, impotence, orthostatic hypotension

Table 3 Proposed neuroprotective agents for chemotherapy toxicity

Neuroprotective agent	Dose	Chemotherapy drug	Neurotoxicity type
Vitamin E	300 mg b.i.d. P.O. 300 mg qd P.O.	Paclitaxel [41] Cisplatin [46–48]	Peripheral neuropathy
Amifostine	740 mg/m^2 IV before and after chemotherapy	Paclitaxel [39, 40]	Peripheral neuropathy
Thymidine [35]	8 g/m^2/day IV	5-Fluorouracil	Encephalopathy
Methylene Blue [20, 21]	50 mg q6 h IV	Ifosfamide	Encephalopathy
Folinic acid [8]	25 mg q6 h IV	Methotrexate	Encephalopathy

cyclosporine or tacrolimus neurotoxicity (Table 1). A study performed in 290 patients conditioned before transplantation with myeloablative therapy reported neurotoxicity from cyclosporine or tacrolimus in 21 (7.2%) of patients, as confirmed with computed tomography (CT) or MRI [22]. In another study of 121 patients, 61 were randomly assigned to receive tacrolimus and 60 to receive cyclosporine-based immunosuppression prior to transplantation, the incidence of moderate or severe neurotoxicity was markedly higher in patients treated with tacrolimus than cyclosporine [23]. The manifestations of such central neurotoxicity included confusion, aphasia, dystonias, akinetic mutism, parkinsonism, palsies, seizures, catatonia, coma, brain hemorrhage, and cortical blindness. Decreased density of the cerebral white matter was visible by CT in 50% of cases, with the most commonly involved sites being the occipital cortex, the cerebellum, the periventricular substance, and the brainstem. In MRI, high-signal lesions are seen on T2-weighted sequences in the areas that are abnormal by CT. Many risk factors have been reported, including hypomagnesemia, hypocholesterolemia, high-dose glucocorticoid therapy, arterial hypertension, and infections [24, 25].

Fludarabine

Fludarabine has been used to treat leukemias and follicular lymphomas. Its toxicity includes myelosuppression, immunosuppression and sporadic life-threatening neurotoxicity (Table 1), although standard doses of it are considered safe. Progressive multifocal leukoencephalopathy caused by JC virus after standard-dose fludarabine has also been described [26, 27]. In addition, a severe neurotoxicity syndrome has been described at doses greater than 40 mg/m^2/day, characterized by blindness, encephalopathy, and coma, due to a diffuse, necrotizing leukoencephalopathy which was most severe in the occipital lobes [28, 29].

Cytarabine (cytosine arabinoside, Ara-C)

In a case report, a patient with acute myeloid leukemia treated with standard doses of cytarabine chemotherapy who developed reversible posterior leukoencephalopathy syndrome suggesting not only a direct cerebral neurotoxicity of cytarabine, but also a possible allergic response as a contributing factor in the development of leukoencephalopathy (Table 1) [30]. Administration of high-dose cytarabine has been associated primarily with acute cerebellar syndrome and secondary with diffuse cerebral dysfunction and MRI findings of high-intensity lesions in the central white matter on T2-weighted MR that may reverse with resolution of the clinical syndrome [31]. The cerebellar toxicity associated with high-dose Ara-C seems to increase with age and may become irreversible at ages over 55 years [32]. However, high-dose cytarabine, in addition to severe cerebellar toxicity, may result in cranial neuropathies due to subacute involvement of brainstem and spinal motor neurons. Pathology in such cases demonstrated hypereosinophilic perikarya and karyolytic nuclei resulted from accumulations of argyrophilic masses of filaments that stained positively with neurofilament antibodies and ultrastructurally were shown to be composed of bundles of intermediate filaments [33].

5-Fluorouracil (5-FU)

Encephalopathy is a form of neurotoxicity of 5-FU manifested as episodes of confusional state and abnormalities of symmetrically restricted diffusion in the periventricular white matter (Table 1) [34]. These side-effects could be reversible upon discontinuation of the chemotherapeutic agent. Patients with decreased dihydropyrimidine dehydrogenase (DPD) activity are at increased risk for experiencing serious neurological toxicity following 5-FU-based chemotherapy. In a case report of a 50-year-old man who developed severe encephalopathy during his second cycle of 5-FU chemotherapy, he showed dramatic improvement following continuous i.v. infusion of thymidine at 8 g/m^2/day (Table 3). Laboratory studies revealed the patient to be severely DPD deficient, suggesting that cancer patients with DPD deficiency may be at increased risk for developing severe neurological toxicity secondary to 5-FU chemotherapy, and that infusional thymidine should be considered as a potential rescue agent against this particular host toxicity [35]. In addition, the 5-FU induced neurotoxicity may include an acute, usually reversible cerebellar syndrome [36].

Peripheral neuropathy with 5-FU therapy has only rarely been reported (Table 2). Two patients treated in a phase I trial of oral 5-FU, leucovorin and eniluracil, an inhibitor of DPD, developed sensorimotor polyneuropathy. The neurological condition of these patients stabilized after 5-FU dose reduction and partial resolution gradually occurred when protocol therapy was stopped. Since DPD was profoundly inhibited during eniluracil therapy in these two patients, it is likely that 5-FU or its active metabolites were contributing factors to the peripheral neuropathy [37].

Taxanes

Taxanes are antineoplastic agents that promote the assembly of microtubules as well as stabilizing their formation by preventing depolymerization. Myelosuppression was found

to be dose-limiting, but peripheral neurotoxicity is also a well known side-effect. Taxanes produce a symmetric, axonal mixed, predominantly sensory, distal neuropathy (Table 2). There is currently no effective symptomatic treatment for paclitaxel-associated pain secondary to neuropathy, but tricyclic antidepressants and anticonvulsants have been used as symptomatic treatment with some success [38]. In an in vitro study, using the rat pheochromocytoma cell line PC-12 neurite-outgrowth assay, the potential of amifostine to protect against various chemotherapeutic agents-induced neurotoxicity was investigated. Amifostine protected against paclitaxel-induced neurotoxicity, but not against vincristine-induced neurotoxicity (Table 3) [39]. However, administration of amifostine (740 mg/m^2) before and 12 h after initiation of high-dose paclitaxel infusion failed to prevent or reduce the neurotoxicity [40]. In the contrary, a small prospective randomized trial in 32 patients undergoing 6 courses of paclitaxel-based chemotherapy found that vitamin E (300 mg twice a day) protected most patients from the occurrence of paclitaxel-induced peripheral neuropathy [41]. CNS toxicity is extremely rare [42], probably because paclitaxel does not cross the blood–brain barrier (Table 1) [43]. However, paclitaxel may cause severe acute transient encephalopathy, especially after prior whole brain radiotherapy and/or surgery, probably due to alteration of small vessel integrity [44].

Cisplatin/oxaliplatin

Cisplatin is used to treat many types of solid tumors. However, it is neurotoxic, and most of the patients completing a full course of cisplatin chemotherapy develop a clinically detectable sensory neuropathy (Table 2). In order to estimate the incidence and prognosis of cisplatin-induced neurotoxicity, 29 patients with metastatic disease were studied prospectively with measurement of sural nerve sensory action potential and conduction velocity and vibration threshold in the left big toe. At the end of chemotherapy (3–4 cycles), only 3 out of 26 (11%) patients had paresthesia, but 3 months later, the proportion rose to 65%. Vibration thresholds showed a significant deterioration during chemotherapy, further deterioration in the 3 months following chemotherapy and significant improvement between 3 and 12 months after chemotherapy [45]. In a randomized study in 47 patients who received cisplatin chemotherapy, a group of patients received vitamin E supplementation during cisplatin chemotherapy, and another group did not. Alpha-tocopherol (vitamin E, 300 mg/day) was administered orally before cisplatin chemotherapy and continued for 3 months after the suspension of treatment. Supplementation of patients receiving cisplatin chemotherapy with vitamin E decreased the incidence and severity of peripheral neurotoxicity (Table 3) [46]. Similar results were also reported in animal tumor models [47]. Although the mechanism of vitamin E-mediated neuroprotection is not entirely known, there are similarities between clinical and neuropathological aspects in peripheral neuropathy induced by cisplatin and vitamin E deficiency. In addition, patients treated with cisplatin demonstrate decrease in the serum levels of vitamin E [48]. It is possible that an inadequate amount of the antioxidant vitamin E due to cisplatin treatment may be responsible of the peripheral nerve damage induced by free-radicals [48].

Cisplatin may occasionally cause reversible posterior leukoencephalopathy syndrome manifested by bilateral reversible abnormalities in the occipital, parietal, and frontal white matter (Table 1) [49]. Acute blindness or seizures are usually the first signs of central neurotoxicity from cisplatin. In cases of subacute neurotoxicity caused by cisplatin, progressive encephalopathy and partial loss of vision were the main observed signs [50].

Oxaliplatin, a platinum derivative currently used in combination with 5-FU to treat colorectal cancer, induces an acute neurotoxicity manifested as distal dysesthesias as well as chronic sensory peripheral neuropathy (Table 2) [51]. The pain syndrome induced by oxaliplatin may be produced by the toxicity of the drug to the IB4-positive neurons of the dorsal root ganglia of the spinal cord [51]. In a recent study, use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity resulted in lower response rate and the combined oxaliplatin neuropathy prevention trial (CONCEPT) was prematurely terminated [52]. However, other investigators reported better neurotolerance and no impact of calcium and magnesium salts on oxaliplatin activity [53]. Another neuroprotective agent that may have some effect against oxaliplatin-induced neurotoxicity is xaliproden, although its effect seems to be marginal and currently is under ongoing investigation [54].

Thalidomide

Thalidomide is active in advanced relapsed and refractory multiple myeloma and its use has been proposed either in newly diagnosed patients or as maintenance treatment after conventional or high-dose therapy. Side-effects related to thalidomide include neuropathy (Table 2), constipation, edema, bradycardia, skin reactions, cerebrovascular events and deep vein thromboses. The mixed sensory-motor, predominantly sensory axonal neuropathy of thalidomide is usually common, but mild [55] and can be monitored by following the measurement variations in sural nerve sensory action potential amplitude [56]. Although this electrophysiological parameter provides information about subclinical neurotoxic potential of thalidomide, it is not

helpful in predicting the appearance of sensory symptoms [56]. Thus, electrophysiologic monitoring provides no clear benefit versus careful clinical evaluation for the development of clinically significant neuropathy [57]. The findings of the frequent appearance of neuropathy in patients treated with thalidomide suggest that long-term thalidomide therapy may be hampered, and that a neurological evaluation should be mandatory prior to treatment [58].

Conclusions

Advances in systemic chemotherapy have extended survival and improved the quality of life of patients with cancer. Despite this progress, many effective chemotherapy drugs have to be discontinued or significantly reduced in dosages because of neurotoxicity. However, the most important issue is early recognition of neurotoxicity in order to avoid continuous use of responsible chemotherapy and irreversible damage. Some agents, such as vitamin E, seem to exert some protective properties for peripheral nerve injury induced by cisplatin or taxanes. Other agents, such as thymidine for 5-FU, methylene blue for ifosfamide and folinic acid for methotrexate may minimize encephalopathy induced by these chemotherapies. Several other potentially neuroprotective agents are currently under investigation. Pre-treatment evaluation by a neurologist is recommended if there are symptoms or conditions pointing to pre-existing peripheral neuropathy or CNS involvement. In addition, neurological evaluation should be performed regularly during chemotherapy with neurotoxic agents.

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