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Chemotherapy-Related Neurotoxicity

Sophie Taillibert[1] · **Emilie Le Rhun**[2,3,4] · **Marc C. Chamberlain**[5]

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Abstract Chemotherapy may have detrimental effects on either the central or peripheral nervous system. Central nervous system neurotoxicity resulting from chemotherapy manifests as a wide range of clinical syndromes including acute, subacute, and chronic encephalopathies, posterior reversible encephalopathy, acute cerebellar dysfunction, chronic cognitive impairment, myelopathy, meningitis, and neurovascular syndromes. These clinical entities vary by causative agent, degree of severity, evolution, and timing of occurrence. In the peripheral nervous system, chemotherapy-induced peripheral neuropathy (CIPN) and myopathy are the two main complications of chemotherapy. CIPN is the most common complication, and the majority manifest as a dose-dependent length-dependent sensory axonopathy. In severe cases of CIPN, the dose of chemotherapy is reduced, the administration delayed, or the treatment discontinued. Few treatments are available for CIPN and based on meta-analysis, duloxetine is the preferred symptomatic treatment. Myopathy due to corticosteroid use is the most frequent cause of muscle disorders in patients with cancer.

Keywords Chemotherapy · Neurotoxicity · Encephalopathy · Chemobrain · Chemotherapy-induced peripheral neuropathy · Myopathy

Sophie Taillibert and Emilie Le Rhun are co-first authors

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✉ Marc C. Chamberlain
marccchamberlain@gmail.com

[1] Department of Neurology 2. Pitié-Salpétrière Hospital, Assistance Publique des Hôpitaux de Paris (APHP), University Pierre and Marie Curie, Paris VI, Paris, France

[2] Neuro-oncology, Neurosurgery Department, University Hospital, Lille, France

[3] Neurology, Medical Oncology Department, Oscar Lambret Center, Lille, France

[4] Lille University, INSERM U1192, Villeneuve d'Ascq, France

[5] Department of Neurology and Neurological Surgery, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, University of Washington, 825 Eastlake Ave E, Seattle, WA 98109, USA

Introduction

With improvement of cancer therapy, there are increasing numbers of long-term cancer survivors. Consequently, it is important to address chemotherapy-induced toxicities, many of which are chronic and persist following treatment discontinuance. Chemotherapy-related neurotoxicity may involve either the central (CNS) or the peripheral nervous system (PNS) adds a considerable burden and severely impacts patient quality of life. Moreover, chemotherapy-related neurotoxicities are dose-limiting and may lead to a treatment discontinuation, thus negatively impact the therapeutic efficacy of cancer treatment. There is an increasing research effort in chemotherapy-related neurotoxicity; however, currently, there is a lack of preventative or therapeutic therapies.

In this review, we endeavor to summarize mechanisms and management of neurological complications resulting from chemotherapy. As the topic is extensive, categories of neurotoxicity are displayed in tabular form, and the text discusses the clinically most relevant toxicities for which specific aspects of the etiopathogenesis, diagnosis, and management are best described. Moreover, the review highlights complications that if recognized early allow for timely management of symptoms, adjustment of drug dosing, and discriminating between iatrogenic effects of cancer therapy and neurological

progression due to cancer. For clarity, the side effects of chemotherapy occurring in the CNS and in the PNS are described separately, with an emphasis on long-term cognitive impairment and peripheral neuropathy, both highly detrimental and illustrative of chronic chemotherapy-related neurotoxicity. Recent literature suggests the existence of shared mechanisms and relationships between these common neurotoxicities [1••, 2•].

Methodology

Using the PubMed database, studies and reviews published regarding the neurotoxicity of chemotherapy were identified by using the search terms "chemotherapy" (or more specifically by agent) combined with the following terms: "neurotoxicity, neurologic complications, CNS, PNS, cognitive impairment, chemobrain, encephalopathy, cerebellar syndrome, posterior reversible encephalopathy, meningitis, neurovascular complications, myelopathy, peripheral neuropathy, myopathy." Prospective and large retrospective studies were used whenever possible and primarily those publications from 2011 to the present. Older references were used when not referred to in a more recent article or review.

Central Nervous System

Encephalopathy

Encephalopathy is the most common chemotherapy-related toxicity affecting the CNS and may manifest as an alteration of consciousness, seizure, neurobehavioral disturbance, or focal neurological deficits [3–5]. A variety of chemotherapy agents may be causative; the most relevant are detailed in Table 1. Acute encephalopathy presents proximate to chemotherapy administration whereas subacute encephalopathy is seen 1 week to 6 months posttreatment. Delayed encephalopathy is observed >6 months after treatment completion [2•]. The differential diagnosis of encephalopathy includes causes other than chemotherapy (for example, metabolic/endocrine disturbances, CNS infection and metastatic disease to the CNS) that require investigation and appropriate treatment when identified [3–5].

Systemic high-dose methotrexate (MTX) is illustrative as MTX can cause acute, subacute, or chronic encephalopathy (Table 1). The acute syndrome (generally altered mental status) is reversible and does not contraindicate further treatment [6]. A subacute "stroke-like" syndrome, characterized by transient (<72 h) focal neurologic deficits, confusion, and occasionally seizures can occur within days to weeks after treatment [12]. Delayed leukoencephalopathy is most often manifest radiographically wherein MRI shows diffuse white matter hyperintensities on T2-weighted/fluid attenuation inversion recovery (FLAIR) sequences and brain parenchymal volume loss. Leukoencephalopathy may be asymptomatic or range from mild cognitive impairment to a progressive dementia with ataxia, alteration of consciousness, seizures, and focal deficits [6]. The occurrence of leukoencephalopathy is in part related to the total cumulative dose of MTX and previous CNS-directed radiotherapy. Homocysteine toxicity, altered folate homeostasis, and direct neuronal damage have been posited as causal mechanisms of MTX neurotoxicity [56]. Dextromethorphan, an antagonist of N-methyl-D-aspartate (NMDA) receptors, has been proposed as a treatment in that homocysteine is an agonist of NMDA receptors [57].

A minority of patients (as many as 30 %) treated with ifosfamide develop an acute encephalopathy within hours or days of administration. Risk factors include a prior history of ifosfamide-related encephalopathy, schedule of administration (non-continuous intravenous administration), renal impairment, low serum albumin, or concomitant administration of aprepitant [7, 8]. Movement disorders, an extrapyramidal syndrome, ataxia, myoclonus, and complex partial status epilepticus can be observed [9, 10]. Ifosfamide-related encephalopathy is usually spontaneously reversible, and methylene blue is often administered as a treatment. Methylene blue is believed to inhibit ifosfamide metabolites that result in oxidative mitochondrial toxicity, inhibits amine oxidase activity, and prevents formation of the neurotoxic chloroacetaldehyde metabolite [58].

Cisplatin-induced encephalopathy is rare, occurs primarily with intra-arterial administration and is related to selective arterial streaming within the CNS resulting in focal neurological deficits [4]. Encephalopathy due to 5-fluorouracil (5FU) manifests radiographically as transient multifocal contrast enhancing lesions associated with elevated serum ammonia levels [11]. Patients who lack the catabolic enzyme dihydropyrimidine dehydrogenase (DPD) are at increased risk [59].

The combination of CNS-directed radiation therapy and chemotherapy appears to result in more frequent and severe instances of leukoencephalopathy although no comparative study is available [13]. Particularly notable are instances of disseminated necrotizing leukoencephalopathy observed in primary CNS lymphoma patients following treatment with high-dose MTX and whole brain irradiation [13]. Agents other than MTX that manifest synergistic radiation-associated cognitive toxicity include cytarabine, nitrosoureas, cisplatin, etoposide, or dactinomycin. As a consequence, MTX should be avoided after whole brain irradiation whenever possible, and prospective cognitive evaluation should be considered in clinical trials combining radiotherapy and chemotherapy for CNS tumors [13].

Table 1 Central nervous system toxicities of chemotherapy agents

Nature (reference)	Drugs	Clinical and radiographic findings	Differential diagnosis
Acute encephalopathy [3–11]	Intra-CSF methotrexate Intra-CSF cytarabine Intravenous high-dose methotrexate Intravenous high-dose thiotepa 5-FU (hyperamoniema) Capecitabine, ifosfamide Cisplatin: (intraarterial > intravenous) Mitomycine C, high-dose fludarabine, high-dose BCNU, high-dose etoposide, high-dose L-asparaginase, high-dose pentostatine, nelarabine, vincristine, gemcitabine, chlorambucil, paclitaxel, procarbazine	Seizures, confusion, disorientation, lethargy	Deficiency in thiamine (Wernicke) metabolic hyponatremia, hyperammonemia, organ failure Infections : CNS or systemic CNS progression, tumor, CSF flow obstruction + hydrocephalus Paraneoplastic syndrome Treatment-related: Steroids, antibiotics, anticonvulsants, pain-killers, narcotics, antiemetics (ondensetron and aprepitant), anticancer targeted therapies, and immunotherapy, CNS irradiation, overmedication
Acute/subacute encephalopathy [3–6, 12]	Intra-CSF methotrexate High-dose intravenous methotrexate Cisplatin	Stroke-like syndrome Normal CSF MRI: restricted diffusion	Stroke
Delayed, chronic, leukoencephalopath [3–6, 13]	High risk if intra-CSF cumulative dose of methotrexate >140 mg Combined radiation therapy with high-dose intravenous/intra-CSF chemotherapy Combined radiation therapy + chemotherapy: methotrexate, aracytine, cisplatin, etoposide, nitrosoureas, dactinomycin High-dose pentostatin, high-dose fludarabine, hydroxyurea	Subcortical-frontal syndrome, mutism-akinetism CSF:↑protein MRI: cortical atrophy, diffuse white matter ↑ T2W and FLAIR signal, ventricular dilatation	
Posterior reversible (leuko) encephalopathy (PRES) [13]	Intra-CSF methotrexate, Cytarabine, gemcitabine, ifosfamide, paclitaxel, vinflunine, vincristine, cisplatin, carboplatin, oxaliplatin, cyclophosphamide	Headache, visual field deficit, change in mental status and seizures. MRI: reversible cortical and subcortical high-signal lesions on T2-W and FLAIR sequences usually without enhancement, ↓ signal intensity on diffusion-weighted and ↑ apparent diffusion coefficient MRI	Anticancer therapies, toxic and metabolic, encephalitis, venous thrombosis, stroke
Chronic cognitive impairment [14–25, 26•, 27, 28••, 29–37]	Potentially all systemic chemotherapy regimens	MRI: ↓ gray and white matter volume in the frontal-temporal lobes fMRI: ↓ bilateral anterior frontal/left anterior cingulate cortex activation during multitasking and ↑ activation in the posterior frontal and parietal lobes	Cancer treatment-related: hormonal therapy, targeted anticancer therapies, CNS irradiation
Acute pancerebellar syndrome [4, 38]	High-dose intravenous cytarabine (>3 g/m^2) Capecitabine 5-FU (subacute > acute), vincristine (rare)	Encephalopathy followed by pan-cerebellar syndrome MRI: cerebellar atrophy, reversible and diffuse leukoencephalopathy	Vitamin B1 deficit Tumor invasion Vascular Paraneoplastic
Aseptic meningitis [4, 39–42]	Any intra-CSF chemotherapy	Mimics bacterial Meningitis CSF: pleocytosis, ↑ protein	Bacterial or fungal meningitis, Subarachnoid hemorrhage
Bacterial and fungal meningitis [4, 40, 42–44]	Any intra-CSF chemotherapy		
CNS infections: CMV, HHV-6, fungal, [4, 40, 44]	High-dose regimen/post-transplant (0–1 month)		
CNS infections: HSV, toxoplasmosis, VZV [4, 40, 44]	High-dose regimen/post-transplant (1–6 months)		
CNS infection: VZV, progressive multifocal leukoencephalopathy [4, 40, 44]	High-dose regimen post-transplant (>6 months)		

Table 1 (continued)

Nature (reference)	Drugs	Clinical and radiographic findings	Differential diagnosis
Neurovascular 0–1 month [4, 45, 46]	Intracranial hemorrhage: L-asparaginase, intraventricular device Stroke (arterial ischemia): cisplatin, intra-CSF or intravenous high-dose methotrexate, cyclophosphamide, 5-FU Sinus/cortical vein thrombosis: L-asparaginase Thrombotic microangiopathy: mitomycin C, gemcitabine Subdural hematoma: high-dose regimen Epidural hematoma: any intra-CSF chemotherapy with thrombocytopenia Subarachnoid hemorrhage: high-dose regimen, any chemotherapy inducing thrombocytopenia		Leukemic cell infiltration, disseminated intravascular coagulation, dehydration, sepsis-related coagulopathy, disseminated aspergillosis, mucormycosis, fungal mycotic aneurysm, brain metastases spontaneous bleeding, choriocarcinoma, intraventricular device, antiangiogenic agents
Headache 0–1 month [4]	Capecitabine, fludarabine, high-dose methotrexate, hydroxyurea, intra-CSF cytarabine, intra-CSF methotrexate, nelarabine, mechlorethamine, temozolomide		Venous thrombosis, any cause of intracranial hypertension, CNS tumor progression, intracranial or subarachnoid hemorrhage, intra-CNS infection, posterior reversible leukoencephalopathy syndrome
Seizures (without associated encephalopathy) 0–1 month [4, 47]	High-dose busulfan, 5-FU, cisplatin, paclitaxel, ifosfamide, paclitaxel, ifosfamide, intra-CSF methotrexate, etoposide, chlorambucil, gemcitabine, carmustine wafer, hydroxyurea, nelarabine, vincristine		CNS progression, pseudo-progression (necrosis), CNS infections
SIADH [4]	Cisplatin, Vincristine, cyclophosphamide		
Extrapyramidal syndrome (dystonia/abnormal movements) [4]	5-FU, doxorubicin, cytarabine, ifosfamide		
Transient cortical blindness [4]	Etoposide, vincristine, cisplatin, high-dose fludarabine		Stroke
Other: encephalitis, seizures, visual loss, communicating hydrocephalus, pseudotumor cerebri-like syndrome, conus medullaris/cauda equine syndrome, radiculopathy, [4, 48]	Whole brain irradiation + high-dose intravenous or intra-CSF methotrexate or liposomal cytarabine		
Myelopathy [4, 39, 49–55]	Intra-CSF: methotrexate most frequent Intra-CSF AraC, liposomal-cytarabine, thiotepa less frequent Intravenous cisplatin± high-dose carmustine nelarabine With most agents, previous intra-CSF treatments or radiation increase risk	Back pain followed by paraparesis, poor clinical evolution after methotrexate with 60 % irreversible paraparesis. Clinical evolution is variable with the other drugs (from reversible to irreversible) CSF:↑protein MRI: spinal cord swelling,↑T2WI signal, ±contrast-enhancement	Immunotherapy (ipilimumab), epidural metastases, compressive epidural hemorrhage or hematoma after lumbar puncture (thrombocytopenia), delayed progressive and irreversible post-spinal irradiation, paraneoplastic disorders, chronic steroid-related epidural lipomatosis

CNS central nervous system, *5-FU* 5-fluorouracil, *CMV* cytomegalovirus, *CSF* cerebrospinal fluid, ↓ decreased, ↑ elevated, *FLAIR* fluid attenuation inversion recovery, *Gd* gadolinium, *HHV* human Herpes virus, *HSV* Herpes simplex virus, *MR* magnetic resonance, *fMRI* functional magnetic resonance imaging, *T2WI* T2 weighted-images, *VZV* varicella-zoster virus, *SIADH* syndrome of inappropriate ADH

Posterior Reversible Encephalopathy Syndrome

A number of cancer agents may cause a posterior reversible encephalopathy syndrome (PRES) (Table 1) [60]. Headache, seizures, altered state of consciousness, and visual disturbances (hemianopia, hallucinations, cortical blindness) are the main clinical features [60, 61]. Hypertension is frequent, regardless of the etiology, but not invariant and may precede

the neurologic syndrome. MRI demonstrates symmetric parieto-occipital T2/FLAIR white matter hyperintensities, but topographic variations often occur [62]. The precipitating event is acute endothelial cell damage resulting in a cerebral microangiopathy, cerebrovascular dysregulation, and vasogenic edema. Lowering of blood pressure, supportive care, and discontinuance or at least reduction of the causal drug are the mainstay of the treatment. Resolution of PRES is anticipated within weeks. Reintroduction of the causative agent should be avoided as recurrence of PRES may occur [62].

Long-Term Cognitive Impairment

With an increase in long-term cancer survivors, persistent post-chemotherapy cognitive impairment has been increasingly observed particularly in breast cancer patients after adjuvant chemotherapy and in hematological malignancies. The reported incidence is 15 to 50 % and, cognitive impairment may persist years after treatment [14]. Moreover, in a small subset of patients, continued cognitive decline over time following treatment has been reported [14, 15].

This entity termed "chemobrain" or "chemofog" consists of a decline in memory, attention, and executive functions (processing speed, verbal and visuospatial abilities, multitasking, goal-directed behavior) [15–17]. The syndrome is independent of depression, anxiety, or fatigue, which are nonetheless disorders considered in the differential diagnosis. The entity of chemobrain remains challenging to diagnose due to a lack of a standardized definition and method of cognitive assessment; discrepancies between subjective complaints by patients and objective testing; lack of longitudinal analysis with baseline cognitive evaluation; heterogeneity of cancer treatments; presence of confounding factors such as associated treatment (hormonal therapy, surgery, and radiation); host-related factors (genetics, educational level, age, cognitive reserve, immune and inflammatory status, menopause, fatigue, and other comorbidities); and disease-related factors (disease status, chronic graft versus host disease, cytokines, and tumor genetics) [15, 17, 18]. Furthermore, the presence of significant cognitive impairment at time of diagnosis before treatment is seen in 20–30 % of leukemia patients, 15–75 % of breast cancer patients, and 45 % of colon cancer patients compound the difficulty in rendering a diagnosis. In colon cancer patients, cognitive impairment persisted over time (2 years after treatment completion) and was not related to chemotherapy [19, 20].

Hypothesis as to causation include genetic vulnerability such as polymorphisms of apolipoprotein E4 (APOE4) allele) and catechol-O-methyltransferase (COMT) genotype that may predispose to post-chemotherapy cognitive impairment [21–23]. Patients with certain specific single nucleotide polymorphisms (SNPs) in the promoter region of proinflammatory cytokines appear also to be at greater risk for cognitive complaints [24]. Cytokine deregulation may play a role, with studies showing that increased serum tumor necrosis factor- and decreased interleukin-6 levels are correlated with smaller hippocampal volume and lower verbal memory performances in breast cancer patients previously treated with chemotherapy [25]. Significant elevations of the soluble proinflammatory cytokine tumor necrosis factor receptor 2 are reported in association with adjuvant chemotherapy and radiation exposure in breast cancer patients [18, 26•]. These levels fall during the 12 months after conclusion of adjuvant chemotherapy, and as systemic levels normalize, there is also normalization of cerebral metabolism by brain imaging [18, 26•]. In contrast, no correlation was found between the elevated cytokines levels and cognitive impairment in colon cancer patients [20]. Chemotherapy might also accelerate the aging process through free radical production, accumulation of DNA damage, decrease in telomerase activity, inhibition of DNA repair, and immunological dysfunction [17, 18].

Brain imaging studies performed mostly in breast cancer patients who received adjuvant treatment have consistently shown lower gray and white matter volume particularly in the frontal and temporal lobes [22, 25, 28••, 29–31]. These MRI structural changes have been correlated to self-reported difficulties and objective impairment in executive function and memory performance, and to cytokines levels [18, 22]. Decrease in fractional anisotropy in the fronto-parieto-occipital lobes may explain reduced attention through impairment of network connectivity [27, 28••]. Functional imaging demonstrates a pattern of decreased anterior frontal cortex activation and increased activation in posterior frontal regions during multi-tasking [28••]. These findings were correlated with subjective and objective executive impairment and may reflect impaired working memory and associated compensatory mechanisms (recruitment of broader networks to obtain the same performance level as controls) [28••]. It has been proposed that these findings explain the frequent dissociation between subjective cognitive complaints and objective performance that are often within normal limits [19].

No specific treatment has been established notwithstanding studies involving the use of modafinil, methylphenidate, and donepezil. Differing cognitive and behavioral interventions, including some based on computerized tools and some group-based, aimed at developing compensatory strategies, have been recently evaluated and may be of some utility [17, 32–35]. In breast cancer patients, a sustained improvement in self-reported cognitive complaints, objective neuropsychological test performance, was observed with a normalization of electroencephalography (EEG) patterns in the intervention group as compared with the control group [32, 33, 36]. It has been suggested that EEG may be a useful biomarker of cognitive changes and may have utility in the prospective assessment of this disorder [18, 37]. Patients have variable

cognitive reserve at the time of cancer diagnosis that likely influences the cognitive impact of cancer treatment [18]. Consequently, host factors and individual vulnerability may be just as important as treatment in causing chronic cognitive impairment [18].

Acute Pancerebellar Syndrome

An acute pancerebellar syndrome is most often secondary to high-dose cytarabine (incidence 30 %) or 5-FU but may occur with other agents (Table 1) [4, 38]. The differential diagnosis of an acute pancerebellar syndrome includes brain metastases as well as paraneoplastic disorders. Risk factors for cytarabine-associated cerebellar syndrome include age over 40 years, abnormal liver or renal function, underlying neurologic impairment, and total cumulative cytarabine dose of >30 g. Clinical onset is most often within the first week but may be delayed for several weeks. A diffuse encephalopathy usually precedes the cerebellar syndrome. MRI is typically normal though occasional diffuse FLAIR/T2 hyperintensities are present. Cytarabine should be discontinued. Clinical improvement is variable and may be totally or partially reversible or irreversible [38]. Less frequently, a cerebellar syndrome of acute onset and delayed occurrence may occur after 5-FU administration. The syndrome is dose-dependent and usually spontaneously reversible with supportive care. 5-FU should be discontinued as re-challenge often results in reappearance of the syndrome. Patients who lack DPD are at increased risk [59].

Aseptic Meningitis

The most common toxicity of intra-CSF chemotherapy is a treatment-related transient aseptic meningitis or arachnoiditis [4, 39–42]. Clinical features, common to all meningitic syndromes, include fever, headache, nausea, vomiting, meningismus, photophobia, and CSF pleocytosis [41]. Most patients are effectively treated with oral antipyretics, antiemetics, and corticosteroids [39]. Resolution of the syndrome typically is within 5 days, but symptoms can be suggestive of an infectious meningitis or progression of leptomeningeal metastases. Rarely, an adhesive arachnoiditis with CSF flow disturbance, ultimately culminating in a communicating hydrocephalus can occur [39, 40].

CNS Infection

Bacterial or fungal meningitis is an iatrogenic complication of ventricular access devices (VADs) similar to that seen with vascular access devices [4, 40, 43, 44]. The incidence of infection with VADs is approximately 10 % and mainly due to *Staphylococcus epidermidis* [42]. Antibiotics (systemic and intraventricular) may be employed with or without device removal [4, 40].

Immunosuppression is a direct consequence of systemic chemotherapy. CNS (meningeal or parenchymal) infections such as *Candida*, *Nocardia*, *Aspergillus*, *Cytomegalovirus* (*CMV*), *Toxoplasmosis*, *JC virus*, *and herpes viruses* (*HSV*, *HHV-6*, *VHV*) are not infrequent particularly following highly myelosuppressive chemotherapy regimens [4, 40, 44]. Post-transplant patients manifest differing infections according to time from transplant (Table 1).

Neurovascular Complications

Neurovascular complications include arterial ischemia (seen with cisplatin), venous thrombosis and intracranial hemorrhage (L-asparaginase), subarachnoid hemorrhage, subdural hematoma (high-dose regimens resulting in profound thrombocytopenia), and thrombotic microangiopathy (mitomycin) (Table 1) [4, 63]. Neurovascular complications are relatively rare aside from intracranial hemorrhage (mostly subdural) that is observed in up to 20 % of patients with acute leukemia [4].

Cisplatin-induced ischemic strokes are most frequent within 10 days of treatment and following the first cycle of chemotherapy [45]. L-asparaginase causes intracranial hemorrhage in up to 5 % of leukemia patients as a result of superior sagittal sinus or cortical vein thrombosis [4, 45]. Clinical presentation is variable ranging from an isolated headache to severe intracranial hypertension, hemiparesis, seizures, and encephalopathy. Imaging typically shows a hemorrhagic venous stroke. Treatment is both supportive and administration of anticoagulation. As L-asparaginase induces hyperfibrinogenemia and an antithrombin III deficit, antithrombin concentrates and low-molecular weight heparin have also been proposed as treatment [46]. The majority of patients recover from L-asparaginase venous thrombosis; however, 10 % die as a result of this complication. The reintroduction of L-asparaginase is discussed on a case-by-case basis, given the central role of this agent in treating acute lymphoblastic leukemia.

Isolated Neurologic Symptoms

Seizures and headaches are the most frequent isolated neurologic symptoms related to chemotherapy. For example, seizures may be caused directly by chemotherapy (busulfan), or indirectly by hyperhydration (cisplatin), renal impairment (cisplatin, MTX), or by the syndrome of inappropriate ADH (vincristine) [3, 4]. The risk of seizure with busulfan (primarily used as a component of a transplant conditioning regimen) is approximately 10 %, and consequently, seizure prophylaxis is recommended [47].

Myelopathy

Treatment-related myelopathy following intra-CSF chemotherapy is fortunately rare and best characterized with intra-CSF MTX though reported with most commonly used intra-CSF agents (Table 1) [39]. Intra-CSF MTX cumulative doses >50 mg and concomitant or previous spinal radiotherapy, and active CNS disease are established risk factors, but may be absent. Onset is variable (within 48 h to months) after treatment and the prognosis is poor (60 % with residual paraparesis) [49, 50]. Myelopathy may be observed after intra-CSF liposomal cytarabine in 2.5 % of patients regardless of route of administration. Spine MRI may demonstrate increased T2-weighted/FLAIR signal or a contrast-enhancing lesion [51, 52]. Improvement has been reported with steroids, high-dose folic acid, cyanocobalamin, and methionine [53]. Continued intra-CSF chemotherapy is contraindicated in instances of chemotherapy-related myelopathy.

Cisplatin alone or in combination with carmustine can also cause myelopathy. Cases of subacute reversible or irreversible myelopathy have been reported more than 1 month after completion of treatment with nelarabine, particularly when combined with radiotherapy or intra-CSF chemotherapy [54, 55]. Lumbar chemotherapy administration can result in an epidural hematoma resulting in paraplegia in presence of thrombocytopenia or clotting disorders.

Radiculopathy

Isolated radiculopathy related to systemic therapy is rare in cancer patients and is mainly due to re-activation of varicella herpes virus resulting in shingles [4, 48]. The risk of infection in early stage breast cancer patients may be 13- to 25-folder higher than in the general population. Treatment utilizes both analgesics and antiviral medication. Delayed post-herpetic neuralgia may appear in a minority of patients and require opioid treatment. Intra-CSF liposomal cytarabine has been reported to cause a radiculopathy when administered either by a VAD (5 % incidence) or lumbar injection (1.25 % incidence) [39].

Peripheral Nervous System

Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common PNS complication of cancer therapy and can have a significant impact on patient quality of life [64–67]. Permanent symptoms are observed in up to 40 % of patients [64]. In severe cases, the dose of chemotherapy is usually reduced, the administration delayed, or the treatment discontinued [64–69]. The most common chemotherapy agents responsible for CIPN include taxanes (e.g., paclitaxel, docetaxel), vinca alkaloids (vincristine), platinum derivatives (cisplatin, oxaliplatin), epothilones (ixabepilone), halichondrin B analogs (eribulin), proteasome inhibitors (bortezomib), and IMiDs (thalidomide) (Table 2) [70]. The incidence and severity of CIPN is dependent upon the drug regimen, the cumulative dose, the schedule of administration, and neuropathy-related risk factors [68]. Treatment-related risk factors include the class and dose per cycle of chemotherapy, the treatment schedule, cumulative dose, and duration of infusion [48, 53–55, 64–70]. Other risk factors include pre-existing neuropathy due to diabetes mellitus, alcohol, folate/vitamin B12 deficiency, hereditary sensorimotor neuropathy (e.g., Charcot-Marie-Tooth which can be unmasked by neurotoxic chemotherapy exposure) or paraneoplastic neuropathies [64–67, 70]. Prior neurotoxic chemotherapy can also favor the development of CIPN. The role of advanced age of the patient in the development of CIPN is controversial [70]. Pharmacogenomic approaches have identified SNPs that are correlated with the time to onset and the severity of neurotoxicity to specific chemotherapy agents and might in the future assist in determining a patients' risk of neurotoxicity. Genes implicated by SNP analysis include those involved in drug metabolism and cell cycle control [67]. Further studies are needed to confirm the relevance of these SNP associations and their clinical utility.

Symptoms of CIPN can occur after the first cycle of chemotherapy or more frequently after successive cycles [66, 70]. The clinical presentation of CIPN is similar although some differences may be observed among the differing chemotherapy agents (Table 2). Sensory symptoms are most common and include symmetric paresthesia with numbness, tingling, shooting pain, itching, burning, tightness, needle sensations generally in a glove, and stocking distribution. Symptoms of CINP typically begin distally in the digits and migrate centripetally with a predilection for first involving the lower extremities. Hypoesthesia is responsible for loss of hand dexterity whereas loss of proprioception results in ataxia and gait disorders. Pain is a very common symptom of CIPN often requiring treatment. Less commonly, motor or autonomic symptoms are seen. Cranial nerve involvement can be rarely observed [85]. The neurologic examination may reveal decreased sensory perception and loss of deep tendon reflexes. Tests of coordination, Romberg maneuver, or manual recognition of objects can be impaired. Distal weakness and cramps may also be observed in instances of motor involvement. Autonomic signs include orthostatic hypotension, loss of heart rate variability, postural hypotension, constipation, bladder, and bowel disturbance [64, 67, 70].

Electrophysiology studies may help to differentiate the type of neuropathy (axonal versus demyelinating versus neuronopathy). Reduced amplitude of nerve action potentials reflects axonal loss and is the most common electrophysiological finding. Diminished nerve conduction velocity reflecting

Table 2 Incidence, cumulative-dose threshold, clinical features, and outcome for common chemotherapy agents responsible for peripheral neuropathy

Drug	Frequency of CIPN	Threshold of cumulative dose	Clinical particularities	Evolution of CIPN
Docetaxel [65, 66, 70, 71]	All grade: 11–64 % grade 3–4: 1.6–7 %	400–600 mg/m^2	Axonal sensory neuropathy, motor neuropathy reported in less than 5 %, toxic optic neuropathy, associated lymphedema with scleroderma-like lesion, and an associated nerve entrapment	34 % of grade 0-I neuropathy 1 to 3 years after treatment discontinuation, with 15 % reporting a significant impact on quality of life
Paclitaxel [65, 70–72]	All grade: 59–87 % grade 3–4: 7–33 %	200 mg/m^2	Axonal sensory neuropathy, acute neuropathy, associated myalgia, myopathy, arthralgia	All grade CIPN in 41 % of the patients 3 years after treatment discontinuation
Eribulin [73]	All grade 14–44 % grade 3–4: 3–27 %	Dose cumulative ?	Axonal sensori-motor neuropathy, autonomic syndrome	Resolution of symptoms within 12 months
Oxaliplatin [64, 67, 70, 74]	All grade: 20–50 % grade 3–4: 10–20 %	800 mg/m^2	Axonal sensory neuropathy acute neuropathy reported in 85–95 % of the cases with induced cold triggered paresthesia and dyesthesiae in the throat, mouth, face and hands, and motor symptoms such as cramps, jaw spasms, Lhermitte's syndrome	Coasting resolution of symptoms in 80 % in about 6–8 months, but clinically significant symptoms observed 2 to 11 years after treatment discontinuation
Cisplatin [67, 74]	All grade: 20 % grade 3–4: 0.001 %	300–400 mg/m^2	Axonal sensory neuropathy, L'hermitte's syndrome irreversible hearing loss in 19 to 77 % of the cases, permanent tinnitus in 19 to 42 % of the cases, taste and smell disorders, Raynaud syndrome	Coasting asymptomatic or symptomatic neuropathy can be observed 15 years after completion of treatment in 38 and 28 %
Carboplatin [67, 74]	Grade 3–4: 0.002 %	600 mg/m^2	Axonal sensory neuropathy similar to cisplatin-induced peripheral neuropathy	Progression resolution of symptoms after discontinuation
Vincristine [64, 70, 75]	Vinca alkaloids: in 35–45 % vincristine Grade 3–4 sensory neuropathy: 1.6 % Grade 3–4 motor neuropathy: 1.9 %	5–15 mg/m^2	Axonal sensori-motor neuropathy, CN, mononeuropathies, autonomic, muscular symptoms Coasting can be observed in 30 % ocular palsies and vocal cords paralysis	Resolution of symptoms within 2 months Disabling sensory neuropathy reported at 9 years after treatment in 14 % of the patients
Bortezomib [64, 70]	Intravenous all grade: 48–53 % grade 3–4: 6–16 % Subcutaneous all grade: 38–41 % grade 3–4: 4–6 %	1–1.3 mg/m^2	Axonal sensory neuropathy, painful, rarely demyelinating	Resolution of symptoms in 85 % of the cases in a median of 98 days following discontinuation of treatment
Thalidomide [76–84]	All grade: 10–83 %	20 g (total)	Axonal sensory neuropathy	Interruption of treatment in 15 % resolution of neuropathy

demyelination is unusual as most CIPN are axonopathies. Additionally, changes in nerve conduction velocity are often not informative in instances of dorsal root ganglion (DRG) neuronopathies or small fiber sensory neuropathies. Nerve or skin biopsy is rarely indicated but is occasionally used in research protocols [70].

With regard to taxane-related CIPN, the once every 3 weeks regimen of docetaxel has been shown to result in more severe neuropathy than the weekly regimen [65]. Shorter infusions of paclitaxel appear to increase the risk of severe neurotoxicity [64]. The benefit of weekly administration of paclitaxel (versus once every 3 weeks) is controversial with respect to diminishing the incidence of CIPN [64]. The time to improvement in symptoms of neuropathy is significantly shorter following nab-paclitaxel than with paclitaxel or docetaxel [65]. The mechanisms of taxane-induced CIPN include stabilization of microtubules resulting in mitotic arrest and interference with axonal transport, mitochondrial dysfunction, change in gene expression, and increased membrane excitability [66, 72, 73, 86]. Additionally, inflammation of the DRG and peripheral nerve disrupts neurotransmission [66]. A "dying back" pattern of Wallerian degeneration has also been reported [73].

Eribulin, a marine derivative of the marine natural product halichondrin B, is an agent that binds to microtubules and has a deleterious effect on fast axonal transport [73]. The symptoms of neuropathy may worsen after the cessation of chemotherapy especially after cisplatin or oxaliplatin administration, a phenomenon termed "coasting" [67, 70]. The incidence of cisplatin-induced neuropathy increases with higher single dose [64]. Two different clinical forms of CIPN related to oxaliplatin are reported. The acute transient form is observed in 85–95 % of all patients. Oropharyngeal paresthesias and temperature reversal, and sometimes jaw spasms or cramps, are reported. The chronic sensory form, observed in 10 to 20 % of patients, is persistent and dose-dependent [64, 70, 75]. Prolonged infusion duration of oxaliplatin and decreased dose density using weekly dose schedules may reduce oxaliplatin neurotoxicity [64]. Carboplatin is the least neurotoxic platinum derivative [67, 70]. Platinum agents accumulate in the DRG and disrupt nuclear and mitochondrial DNA and consequently result in a neuronopathy. Oxaliplatin has in addition an effect on nodal axonal voltage-gated sodium channels [64, 70]. Impairment of cell surface metal transporters has been reported with oxaliplatin [74].

Vinca alkaloids can result in a dose-related symmetric distal sensorimotor neuropathy [64, 70]. Vincristine and vindesine cause more severe neurotoxicity as compared to vinblastine, vinorelbine, or vinflunine [70]. Liposome-encapsulated vincristine permits administration of higher doses of vincristine without increasing the risk of CIPN [64]. Vinca alkaloids binds to microtubules and affects the interactions of microtubules as well as causing conformational changes (tubulin dimers) thereby impeding axonal transport [70, 73].

Bortezomib, a proteasome inhibitor that can result in a sensory axonal neuropathy, appears to affect both the DRG and peripheral nerve, causes tubulin polymerization, and disrupts endoplasmic reticulum and mitochondrial integrity [64, 70]. Carfilzomib, a new proteasome inhibitor, though neurotoxic is associated with a lower incidence of neuropathy [70].

Thalidomide, an immunomodulatory/antiangiogenic IMiD, may result in an axonal sensory neuropathy that is cumulative dose related. The neuropathy is characterized by paresthesia, numbness, mild motor involvement, and cramps in up to 83 % of patients [64, 70] [76, 77]. After 1 year of treatment, 75 % of patients manifest a CIPN [78, 79]. Thalidomide and other IMiDs result in DRG injury and direct axonal injury [80–82] Long-term thalidomide treatment results in CIPN in 75 % of patients. The thalidomide analogs lenalidomide and pomalidomide induce less neurotoxicity [70]. Lenalidomide induces a severe neuropathy in only 0.9 % as compared to 10.6 % with thalidomide [83] An improvement of neurological symptoms is usually observed within 3–4 months after cessation of treatment [84].

Suramin has also been reported as a cause of an axonal length-dependent sensory-motor and partially reversible CIPN, due to disruption of glycolipid transport and metabolism [87, 88].

A variety of agents have been tried as neuroprotective agents [67, 68, 70, 74, 89••, 90]. A modest mitigating effect on the incidence and severity of CIPN has been reported in randomized trials using L-glutamine and vitamin E [90]. No benefit has however been observed with the use of lipoic acid, nimodipine, gabapentine, lamotrigine, acetyl L-carnitine, venlafaxine, and BNP7787. Inconsistent and generally negative results have been seen with amifostine, glutathione, infusions of calcium, and magnesium. A number of agents nonetheless have been promulgated for the treatment of CIPN including N-Acetylcysteine, carbamazepine and oxcarbazepine, xaliprodenis (a 5-hydroxytryptamine 1A agonist), goshajinkigan (Kampo medicine), erythropoietin, PFT-μ, omega-3 fatty acids supplements, topical gel containing baclofen, amitriptyline, nortriptyline and ketamine, combination vitamin B12/B6, combination vitamin D, and low polyamine diet [67, 68, 70, 74, 89••, 90]. Increased physical activity and exercise has been reported consistently to improve symptoms of CIPN [91]. A Cochrane meta-analysis did not show a neuroprotective effect for any agent for the prevention of platinum-induced CIPN. According to an ASCO clinical practice guideline, there is no standard of care with respect to the treatment of CIPN based on a paucity of prospective randomized trial data [89••].

Detection of CIPN prior the appearance of severe neurologic symptoms is critical [64, 65]. Other causes of neuropathy should be excluded as for example carpal tunnel syndrome [65, 69, 71]. When CIPN is identified, drug discontinuation is recommended for all high-grade neuropathies [65]. Depending upon the severity of the CIPN, the offending agent is usually reduced, delayed, or discontinued [65, 66, 74]. The ASCO guideline concludes the best available treatment option for pain related to CIPN is duloxetine [89••]. Indeed, a phase III randomized, placebo crossover trial showed a significant reduction of pain in patients treated with duloxetine [92••]. Gabapentin or pregabalin is recommended for the treatment of neuropathic pain in CIPN [68]. However, a randomized double-blind, placebo-controlled, crossover trial failed to demonstrate a benefit of gabapentin in the treatment of CIPN symptoms [93]. A Cochrane analysis found little evidence to support the use of venlafaxine in neuropathic pain in CIPN [94]. Other therapeutic options include tricyclic antidepressants, topical amitriptyline, serotonin and norepinephrine reuptake inhibitors opioid narcotics, and topical anasthetics [67, 70, 95, 96]. A Cochrane meta-analysis failed to demonstrate an impact of imipramine in the treatment of neuropathic pain and CIPN [97]. Efficacy of lidocaine infusion on pain due to

CIPN has been reported [98]. Dextromethorphan, a N-methyl-D-aspartate receptor antagonist is currently under evaluation in a randomized double-blind trial in CIPN (NCT02271893). Non-pharmaceutical approaches include acupuncture, non-invasive electroanalgesia device (referred to as "scrambler" therapy), massage, and physiotherapy. They may help to improve gait impairment and assist patients by providing life relevant adaptive strategies [65, 99–101]. A benefit of neurostimulation on chronic painful CIPN resistant to conservative treatment has been reported [102]. Wearing frozen gloves and socks during chemotherapy treatment has been suggested as reducing the risk of developing neuropathy [66].

Myopathy

An acute inflammatory myopathy, with symmetric leg weakness and elevation of serum creatinine phosphokinase caused by docetaxel has been reported [103]. A severe but reversible necrotizing toxic myopathy following capecitabine and oxaliplatin combination has also been reported [104]. Gemcitabine-related myositis has rarely been described [105]. Vinca alkaloids have also been rarely reported as responsible for a necrotizing myopathy [106]. Rhabdomyolysis has rarely been reported following administration of cytarabine, cyclophosphamide, or 5-azacytidine, as well as after bone marrow transplantation [107]. Aromatase inhibitors are commonly responsible for a painful musculoskeletal syndrome that includes arthritis, arthralgia, and myalgia and which can impact long-term compliance with this class of drugs [108]. A recent randomized trial showed an improvement of arthralgia-related to aromatase inhibitors with exercise [109]. The pathophysiology of myopathy related to the abovementioned chemotherapy agents is not well understood.

Steroids which are frequently used as either a chemotherapy agent (as for example in acute lymphoblastic leukemia, lymphoma, and multiple myeloma) or for symptom management (e.g., anorexia or nausea) are the most common agent to cause myopathy, a side effect seen in up to 60 % of patients [110]. Steroid-associated myopathy is in part dependent upon type of steroid, daily and cumulative dose, and duration of steroid treatment [110]. Clinical features include symmetric proximal muscle weakness (particularly iliopsoas and deltoid muscles) and atrophy preferentially involving the lower extremities [111]. Associated dyspnea due to respiratory muscle weakness can be observed [112]. Fluorinated steroids such as dexamethasone or triamcinolone result more often in myopathy than non-fluorinated steroids such as prednisone or hydrocortisone [110]. Acute myopathy has also been reported after the intravenous administration of high-dose steroid [112]. Serum muscle enzyme determination and electromyography are often normal in steroid myopathy [112, 113]. Atrophy of type IIb fibers without necrosis or inflammation is observed by muscle biopsy [113]. Symptoms of myopathy are reversible after reduction or discontinuation of steroids; however, recovery is often prolonged [110]. Physical therapy and exercise is the primary therapeutic option and is recommended when a prolonged treatment regimen is utilized [111].

Conclusion

Chemotherapy regardless of whether administered systemically or intra-CSF has the potential to negatively impact both the central and peripheral nervous system. In certain instances, for example, vincristine, nelarabine, taxanes, and IMiDs, the chemotherapy dose-limiting toxicity is defined by neurotoxicity. Most important however with respect to management of neurotoxicity is early recognition and either chemotherapy dose adjustment or discontinuance as for the vast majority of chemotherapy-related neurotoxicity, there is no specific antidote. Notwithstanding early recognition of neurotoxicity, in some circumstances, neurologic sequelae of chemotherapy persist and require symptom directed management as for example with CIPN and chronic cognitive changes. According to recent data, these two complications often co-occur and have been reported in both to involve the CNS as illustrated by the association between posttreatment CIPN and cerebral perfusion alterations in the brain regions associated with pain processing [2•]. CIPN and cognitive impairment have been hypothesized to be a consequence of neuroinflammation, as well as an underlying genetic susceptibility [1••]. Consequently, improved identification of high-risk patients in whom preventive strategies could be considered, and the development of preventive anti-inflammatory strategies may be among the best therapeutic options in the future [1••]. Better understanding of the mechanisms underlying the pretreatment risk of neurotoxicity may also improve our knowledge of these complications and suggest novel therapies to mitigate this common complication of chemotherapy [1••].

Compliance with Ethical Standards

Conflict of Interest Marc C. Chamberlain declares that he has no conflict of interest.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Ganz PA, Dougherty PM. Painful hands and feet after cancer treatment: inflammation affecting the mind-body connection. J Clin Oncol. 2016;34:649–52. **An updated expert opinion on recent advances regarding chemotherapy –related neurotoxicity, underscoring the important role of inflammation in cognitive dysfunction, and peripheral neuropathy, both linked to neuroinflammation as well as genetic susceptibility to persistent inflammation and behavioral symptoms. The authors also highlight that the symptoms of chemotherapy neurotoxicity can now be measured with a wide variety of well-validated self-report tools i.e. patient-reported outcomes**.

2.• Nudelman KN, McDonald BC, Wang Y, et al. Cerebral perfusion and gray matter changes associated with chemotherapy-induced peripheral neuropathy. J Clin Oncol. 2016;34:677–83. **Longitudinal relationship between chemotherapy-induced peripheral neuropathy (CIPN) symptoms and brain perfusion changes in patients with breast cancer. CIPN symptoms were positively associated with cerebral perfusion in the right superior frontal gyrus and cingulate gyrus, regions associated with pain processing**.

3. Magge RS, DeAngelis LM. The double-edged sword: neurotoxicity of chemotherapy. Blood Rev. 2015;29:93–100.
4. Chamberlain MC. Neurotoxicity of cancer treatment. Curr Oncol Rep. 2010;12:60–7.
5. Hansen N. Drug-induced encephalopathy. In: Tanasescu R, editor. Miscellanea on encephalopathies—a second look. InTech, 2012. pp. 39–60.
6. DeAngelis LM, Posner JB. Side effects of chemotherapy. In: Neurologic complications of cancer, 2nd. New York, Oxford University Press; 2009. p. 447.
7. David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. Am J Clin Oncol. 2005;28:277–80.
8. Hansen H. Aprepitant-associated ifosfamide neurotoxicity. J Oncol Pharm Pract. 2010;16:137–8.
9. Ames B, Lewis LD, Chaffee S, et al. Ifosfamide-induced encephalopathy and movement disorder. Pediatr Blood Cancer. 2010;54:624–6.
10. Savica R, Rabinstein AA, Josephs KA. Ifosfamide associated myoclonus-encephalopathy syndrome. J Neurol. 2011;258:1729–31.
11. Nott L, Price TJ, Pittman K, et al. Hyperammonemia encephalopathy: an important cause of neurological deterioration following chemotherapy. Leuk Lymphoma. 2007;48:1702–11.
12. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. J Clin Oncol. 2014;32:949–59.
13. Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. Lancet. 2009;374(9701):1639–51.
14. Wefel JS, Saleeba AK, Buzdar AU, et al. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer. 2010;116:3348–56.
15. Ahles TA, Saykin AJ, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol. 2010;28:4434–40.
16. Jim HS, Phillips KM, Chait S, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol. 2012;30:3578–87.
17. Moore HCF. An overview of chemotherapy-related cognitive dysfunction, or 'chemobrain'. Oncology (Williston Park). 2014;28:797–804.
18. Ganz PA. Cancer treatment and cognitive function: chemotherapy is not the only culprit. Oncology (Williston Park). 2014;28(9):804–6.
19. Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. J Clin Oncol. 2012;30:3675–86.
20. Vardy JL, Dhillon HM, Pond GR, et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. J Clin Oncol. 2015;33:4085–93.
21. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psychooncology. 2003;12:612–9.
22. McDonald BC, Conroy SK, Smith DJ, et al. Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: a replication and extension study. Brain Behav Immun. 2013;30(Suppl):S117–25.
23. Small BJ, Rawson KS, Walsh E, et al. Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. Cancer. 2011;117:1369–76.
24. Bower JE, Ganz PA, Irwin MR, et al. Cytokine genetic variations and fatigue among patients with breast cancer. J Clin Oncol. 2013;31:1656–61.
25. Kesler S, Janelsins M, Koovakkattu D, et al. Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. Brain Behav Immun. 2013;30(Suppl):S109–16.
26.• Ganz PA, Bower JE, Kwan L, et al. Does tumor necrosis factor-alpha (TNFalpha) play a role in post-chemotherapy cerebral dysfunction? Brain Behav Immun. 2013;30:S99–108. **An exploration of possible mechanisms associated with post-treatment cognitive dysfunction among breast cancer survivors. Cognitive complaints, neuropsychological (NP) test performance, markers of inflammation, and brain imaging were performed. Onlyserum TNF levels was significantly correlated with increased memory complaints and with relatively diminished brain metabolism in the inferior frontal cortex**.
27. Deprez S, Amant F, Smeets A, et al. Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. J Clin Oncol. 2012;30:274–81.
28.•• Deprez S, Vandenbulcke M, Peeters R, et al. Longitudinal assessment of chemotherapy-induced alterations in brain activations during multitasking and its relation with cognitive complaints. J Clin Oncol. 2014;32:20131–8. **Evidence for a relationship between longitudinal changes in cognitive complaints and changes in brain activation after chemotherapy**.
29. de Ruiter MB, Reneman L, Boogerd W, et al. Late effects of high-dose adjuvant chemotherapy on white and gray matter in breast cancer survivors: converging results from multimodal magnetic resonance imaging. Hum Brain Mapp. 2012;33:2971–83.
30. de Ruiter MB, Reneman L, Boogerd W, et al. Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. Hum Brain Mapp. 2011;32:1206–19.
31. McDonald BC, Conroy SK, Ahles TA, et al. Gray matter reduction associated with systemic chemotherapy for breast

cancer: a prospective MRI study. Breast Cancer Res Treat. 2010;123:819–28.
32. Ercoli LM, Castellon SA, Hunter AM, et al. Assessment of the feasibility of a rehabilitation intervention program for breast cancer survivors with cognitive complaints. Brain Imaging Behav. 2013;7:543–53.
33. Ercoli LM, Castellon S, Petersen L, et al. Cognitive rehabilitation group intervention for breast cancer survivors: results of a randomized clinical trial. International Cancer and Cognition Task Force Meeting; Seattle, WA 2014.
34. Schuurs A, Green HJ. A feasibility study of group cognitive rehabilitation for cancer survivors: enhancing cognitive function and quality of life. Psycho-Oncology. 2013;22:1043–9.
35. Cherrier MM, Anderson K, David D, et al. A randomized trial of cognitive rehabilitation in cancer survivors. Life Sci. 2013;93:617–22.
36. Hunter AM, Kwan L, Ercoli LM, et al. Quantitative electroencephalography biomarkers of cognitive complaints after adjuvant therapy in breast cancer survivors: a pilot study. Psycho-Oncology. 2014;23:713–5.
37. Moore HF, Parsons M, Yue G, et al. Electroencephalogram power changes as a correlate of chemotherapy-associated fatigue and cognitive dysfunction. Support Care Cancer. 2014;22:2127–31.
38. Herzig RH, Hines, Herzig GP, et al. Cerebellar toxicity with high-dose cytosine arabinoside. J Clin Oncol. 1987;5:927–32.
39. Chamberlain MC. Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyt) administered for the treatment of leptomeningeal metastases: a retrospective case series. J Neurooncol. 2012;109:143–8.
40. Chamberlain MC, Glantz MJ. Re: neurologic complications associated with intrathecal liposomal cytarabine given prophylactically in combination with high-dose methotrexate and cytarabine to patients with acute lymphocytic leukemia. Blood. 2007;110:1698–9.
41. Chamberlain MC, Kormanik PA, Barba D. Complications associated with intraventricular chemotherapy in patients with leptomeningeal metastases. J Neurosurg. 1997;87:694–9.
42. Zairi F, Le Rhun E, Bertrand N, Boulanger T, Taillibert S, Aboukais R, et al. Complications related to the use of an intraventricular access device for the treatment of leptomeningeal metastases from solid tumor: a single centre experience in 112 patients. J Neurooncol. 2015;124(2):317–23.
43. Pruitt AA. Nervous system infections in patients with cancer. Neurol Clin N Am. 2003;21:193–219.
44. Rosenfeld MS, Pruitt A. Neurologic complications of bone marrow, stem cell, and organ transplantation in patients with cancer. Semin Oncol. 2006;33:352–61.
45. Li SH, Chen WH, Tang Y, Rau KM, Chen YY, Huang TL, et al. Incidence of ischemic stroke post-chemotherapy: a retrospective review of 10,963 patients. Clin Neurol Neurosurg. 2006;108(2):150–6.
46. Hunault-Berger M, Chevallier P, Delain M, et al. Changes in antithrombin and fi brinogen levels during induction chemotherapy with l-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the capelal study. Haematologica. 2008;93:1488–94.
47. Carreras E, Cahn JY, Puozzo C, et al. Influence on Busilvex pharmacokinetics of clonazepam compared to previous phenytoin historical data. Anticancer Res. 2010;30:2977–84.
48. Masci G, Magagnoli M, Gullo G, et al. Herpes infections in breast cancer patients treated with adjuvant chemotherapy. Oncology. 2006;71:164–7.
49. Teh HS, Fadilah SAW, Leong CF. Transverse myelopathy following intrathecal administration of chemotherapy. Singap Med. 2007;48:e46–9.
50. Shintaku M, Toyooka N, Koyama T, Teraoka S, Tsudo M. Methotrexate myelopathy with extensive transverse necrosis: report of an autopsy case. Neuropathol Off J Jpn Soc Neuropathol. 2014;34:547–53.
51. Cachia D, Kamiya-Matsuoka C, Pinnix CC, et al. Myelopathy following intrathecal chemotherapy in adults: a single institution experience. J Neurooncol. 2015;122:391–8.
52. Graber JJ, Nolan CP. Myelopathies in patients with cancer. Arch Neurol. 2010;67:298–304.
53. Ackermann R, Semmler A, Maurer GD, et al. Methotrexate-induced myelopathy responsive to substitution of multiple folate metabolites. J Neurooncol. 2010;97:425–7.
54. Tisi MC, Ausoni G, Vita MG, et al. Clinical reversible myelopathy in T-cell lymphoblastic lymphoma treated with nelarabine and radiotherapy: report of a case and review of literature of an increasing complication. Mediterr J Hematol Infect Dis. 2015;7:e2015025.
55. Gollard RP, Selco S. Irreversible myelopathy associated with nelarabine in T-cell acute lymphoblastic leukemia. J Clin Oncol. 2013;31:327–31.
56. Vagace JM, Caceres-Marzal C, Jimenez M, et al. Methotrexate-induced subacute neurotoxicity in a child with acute lymphoblastic leukemia carrying genetic polymorphisms related to folate homeostasis. Am J Hematol. 2011;86:98–101.
57. Afshar M, Birnbaum D, Golden C. Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity. Pediatr Neurol. 2014;50:625–9.
58. Küpfer A, Aeschlimann C, Cerny T. Methylene blue and the neurotoxic mechanisms of ifosfamide encephalopathy. Eur J Clin Pharmacol. 1996;50(4):249–52.
59. Takimoto CH, Lu ZH, Zhang R, et al. Severe neurotoxicity following 5-fluorouracil-based chemotherapy in a patient with dihydropyrimidine dehydrogenase deficiency. Clin Cancer Res. 1996;2:477–81.
60. Fugate JE, Claassen DO, Cloft HJ, et al. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc. 2010;85:427–32.
61. Kastrup O, Gerwig M, Frings M, Diener HC. Posterior reversible encephalopathy syndrome (PRES): electroencephalographic findings and seizure patterns. J Neurol. 2012;259:1383–9.
62. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. AJNR Am J Neuroradiol. 2002;23:1038–48.
63. Garcia G, Atallah JP Antineoplastic agents and thrombotic microangiopathy. J Oncol Pharm Pract. 2016.
64. Park SB, Goldstein D, Krishnan AV, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. CA Cancer J Clin. 2013;63:419–37.
65. Rivera E, Cianfrocca M. Overview of neuropathy associated with taxanes for the treatment of metastatic breast cancer. Cancer Chemother Pharmacol. 2015;75:659–70.
66. Eckhoff L, Knoop AS, Jensen M-B, Ejlertsen B, Ewertz M. Risk of docetaxel-induced peripheral neuropathy among 1,725 Danish patients with early stage breast cancer. Breast Cancer Res Treat. 2013;142:109–18.
67. Brewer JR, Morrison G, Dolan ME, Fleming GF. Chemotherapy-induced peripheral neuropathy: current status and progress. Gynecol Oncol. 2015. doi:10.1016/j.ygyno.2015.11.011. published online Nov 7.
68. Beijers AJM, Jongen JLM, Vreugdenhil G. Chemotherapy-induced neurotoxicity: the value of neuroprotective strategies. Neth J Med. 2012;70:18–25.
69. Bhatnagar B, Gilmore S, Goloubeva O, et al. Chemotherapy dose reduction due to chemotherapy induced peripheral neuropathy in breast cancer patients receiving chemotherapy in

the neoadjuvant or adjuvant settings: a single-center experience. Springerplus. 2014;3:366.
70. Grisold W, Cavaletti G, Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. Neuro Oncol. 2012;14(4):iv45–54.
71. Osmani K, Vignes S, Aissi M, et al. Taxane-induced peripheral neuropathy has good long-term prognosis: a 1- to 13-year evaluation. J Neurol. 2012;259:1936–43.
72. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol Off J Eur Soc Med Oncol ESMO. 2013;24:2402–8.
73. LaPointe NE, Morfini G, Brady ST, Feinstein SC, Wilson L, Jordan MA. Effects of eribulin, vincristine, paclitaxel and ixabepilone on fast axonal transport and kinesin-1 driven microtubule gliding: implications for chemotherapy-induced peripheral neuropathy. Neurotoxicology. 2013;37:231–9.
74. Avan A, Postma TJ, Ceresa C, et al. Platinum-induced neurotoxicity and preventive strategies: past, present, and future. Oncologist. 2015;20:411–32.
75. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. Cancer Treat Rev. 2008;34(4):368–77. doi:10.1016/j.ctrv.2008.01.003.
76. Kropff M, Giongco-Baylon H, Hillengass J, et al. Thalidomide versus dexamethasone for the treatment of relapsed and/or refractory multiple myeloma: results from OPTIMUM, a randomized trial. Haematologica. 2012;97:784–91.
77. Mileshkin L, Stark R, Day B, et al. Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring. J Clin Oncol. 2006;24:4507–14.
78. Feyler S, Rawstron A, Jackson G, Snowden JA, Cocks K, Johnson RJ. Thalidomide maintenance following high-dose therapy in multiple myeloma: a UK myeloma forum phase 2 study. Br J Haematol. 2007;139:429–33.
79. Tosi P, Zamagni E, Cellini C, et al. Neurological toxicity of long-term(>1 yr) thalidomide therapy in patients with multiple myeloma. Eur J Haematol. 2005;74:212–6.
80. Giannini F, Volpi N, Rossi S, et al. Thalidomide-induced neuropathy: a ganglionopathy? Neurology. 2003;60:877–8.
81. Kirchmair R, Tietz AB, Panagiotou E, et al. Therapeutic angiogenesis inhibits or rescues chemotherapy-induced peripheral neuropathy: taxol- and thalidomide induced injury of vasa nervorum is ameliorated by VEGF. Mol Ther. 2007;15:69–75.
82. Isoardo G, Bergui M, Durelli L, et al. Thalidomide neuropathy: clinical, electrophysiological and neuoradiological features. Acta Neurol Scand. 2004;109:188–93.
83. Gay F, Hayman SR, Lacy MQ, et al. Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma. Blood. 2010;115:1343–50.
84. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354:1021–30.
85. Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: a comprehensive survey. Cancer Treat Rev. 2014;40:872–82.
86. Peng L, Bu Z, Ye X, Zhou Y, Zhao Q. Incidence and risk of peripheral neuropathy with nab-paclitaxel in patients with cancer: a meta-analysis. Eur J Cancer Care (Engl). 2015. doi:10.1111/ecc.12407. published online Nov 4.
87. Chaudhry V, Eisenberger MA, Sinibaldi VJ, Sheikh K, Griffin JW, Cornblath DR. A prospective study of suramin-induced peripheral neuropathy. Brain. 1996;119(Pt 6):2039–52.
88. Gill JS, Windebank AJ. Suramin induced ceramide accumulation leads to apoptotic cell death in dorsal root ganglion neurons. Cell Death Differ. 1998;5(10):876–83.
89.•• Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2014;32:1941–67. **Evidence-based guidance on the optimum prevention and treatment approaches in the management of CIPN in adult cancer survivors**.
90. Pace A, Giannarelli D, Galiè E, et al. Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. Neurology. 2010;74:762–6.
91. Mols F, Beijers AJM, Vreugdenhil G, Verhulst A, Schep G, Husson O. Chemotherapy-induced peripheral neuropathy, physical activity and health-related quality of life among colorectal cancer survivors from the PROFILES registry. J Cancer Surviv Res Pract. 2015;9:512–22.
92.•• Smith EML, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013;309:1359–67. **A randomized, double-blind, placebo-controlled crossover trial demonstrating effectiveness of duloxetine in the treatment of CIPN-related pain**.
93. Rao RD, Michalak JC, Sloan JA, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer. 2007;110:2110–8.
94. Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC. Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;8, CD011091.
95. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007;4, CD005454.
96. Thompson DF, Brooks KG. Systematic review of topical amitriptyline for the treatment of neuropathic pain. J Clin Pharm Ther. 2015. doi:10.1111/jcpt.12297. published online June 7.
97. Hearn L, Derry S, Phillips T, Moore RA, Wiffen PJ. Imipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014;5, CD010769.
98. Papapetrou P, Kumar AJ, Muppuri R, Chakrabortty S. Intravenous lidocaine infusion to treat chemotherapy-induced peripheral neuropathy. Case Rep. 2015;5:154–5.
99. Marineo G, Iorno V, Gandini C, Moschini V, Smith TJ. Scrambler therapy may relieve chronic neuropathic pain moreeffectively than guideline-based drug management: results of a pilot, randomized, controlled trial. J Pain Symptom Manag. 2012;43:87–95.
100. Xu WR, Hua BJ, Hou W, Bao YJ. Clinical randomized controlled study on acupuncture for treatment of peripheral neuropathy induced by chemotherapeutic drugs. Zhongguo Zhen Jiu. 2010;30:457–60.
101. Schroeder S, Meyer-Hamme G, Epplee S. Acupuncture for chemotherapy-induced peripheral neuropathy (CIPN): a pilot study using neurography. Acupunct Med. 2012;30:4–7.
102. Abd-Elsayed A, Schiavoni N, Sachdeva H. Efficacy of spinal cord stimulators in treating peripheral neuropathy: a case series. J Clin Anesth. 2015. doi:10.1016/j.jclinane.2015.08.011. published online Sept 19.
103. Saini R, Chandragouda D, Talwar V, Rajpurohit S. Grade IV myositis: a rare complication of docetaxel. J Cancer Res Ther. 2015;11:664.
104. Orsucci D, Pizzanelli C, Alì G, et al. Nerve, muscle and heart acute toxicity following oxaliplatin and capecitabine treatment. Neuromuscul Disord NMD. 2012;22:767–70.

105. Pentsova E, Liu A, Rosenblum M, O'Reilly E, Chen X, Hormigo A. Gemcitabine induced myositis in patients with pancreatic cancer: case reports and topic review. J Neurooncol. 2012;106:15–21.
106. Bradley WG, Lassman LP, Pearce GW, Walton JN. The neuromyopathy of vincristine in man. Clinical, electrophysiological and pathological studies. J Neurol Sci. 1970;10(2):107–31.
107. Truica CI, Frankel SR. Acute rhabdomyolysis as a complication of cytarabine chemotherapy for acute myeloid leukemia: case report and review of literature. Am J Hematol. 2002;70:320–3.
108. Lintermans A, Van Calster B, Van Hoydonck M, et al. Aromatase inhibitor-induced loss of grip strength is body mass index dependent: hypothesis-generating findings for its pathogenesis. Ann Oncol. 2011;22(8):1763–9.
109. Irwin ML, Cartmel B, Gross CP, et al. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. J Clin Oncol. 2015;33(10):1104–11.
110. Batchelor TT, Taylor LP, Thaler HT, Posner JB, DeAngelis LM. Steroid myopathy in cancer patients. Neurology. 1997;48:1234–8.
111. Roth P, Wick W, Weller M. Steroids in neurooncology: actions, indications, side-effects. Curr Opin Neurol. 2010;23:597–602.
112. van Balkom RH, van der Heijden HF, van Herwaarden CL, Dekhuijzen PN. Corticosteroid-induced myopathy of the respiratory muscles. Neth J Med. 1994;45:114–22.
113. Da Silva JA, Jacobs JWG, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis. 2006;65:285–93.