Neurologic Toxicities of Cancer Therapies

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Neurologic dysfunction is a well-recognized adverse effect of cancer therapeutics. The most common manifestations include peripheral neuropathy and encephalopathy. Often, symptoms resolve or improve upon removal of the offending agent; therefore, it is essential that clinicians recognize the symptoms and signs of injury. Occasionally, symptoms persist or develop after discontinuation of medication and may culminate in disability and diminished quality of life. As our understanding of neurotoxicity improves, medications with less potential for injury may be developed. In addition, potential antidotes to prevent or reverse injury may emerge. This review focuses on the clinical features, mechanisms, and possible therapeutics of the neurotoxicity of chemotherapy. In particular, oxaliplatin, thalidomide, methotrexate, ifosfamide, cytarabine, amifostine, acetyl-L-carnitine, methylene blue, cytokines, and neurotrophins are discussed.

Introduction

Neurotoxicty is a common adverse effect of cancer therapeutics that often represents a dose-limiting side effect. It may lead to disability and decreased quality of life in the absence of tumor progression. Patients must be informed of potential side effects and clinicians must recognize signs and symptoms as they emerge. The objective of this paper is to discuss recent reports of syndromes, mechanisms, and therapeutics of neurotoxicty.

Neuropathy

Peripheral neuropathy is among the most common neurologic side effects of chemotherapy. It represents the dose-limiting toxicity of many oncologic agents (Table 1). Symptoms may be severe and may adversely impact quality of life. Usually, the neuropathies are cumulative and dose related. The type and etiology of neuropathy is dependent on the agent.

Oxaliplatin

Oxaliplatin, the newest platinum agent, has been associated with an acute neuropathic syndrome. Symptoms, described as paresthesias and dysesthesias in the hands, feet, and perioral region, cold hypersensitivity, and uncomfortable laryngeal sensation, usually develop within 1 hour of infusion. Occasionally, patients develop cramps and spasms of limbs and jaw. Typically, symptoms resolve within days, although they may recur and intensify on repeated administration [1]. The acute syndrome is common, affecting 82% to 98% of patients treated with oxaliplatin [1,2]. Fortunately, it does not necessitate drug discontinuation. Nerve conduction studies show transient hyperexcitability with repetitive motor discharges after a single motor neuron stimulation or voluntary activation. Electromyographic evaluation demonstrates repetitive discharges. Sensory nerve conduction is normal. Electrophysiologic changes are transient, usually resolving within weeks of infusion [3•,4].

The mechanism of oxaliplatin-induced acute neuropathy is unknown. Several investigators have attributed this phenomenon to functional alterations in neuronal membrane ion channels. The findings on electromyography and nerve conduction studies closely resemble those found in neuromyotonia, a voltage-gated potassium channelopathy [3]. In vitro studies have demonstrated dysfunction of sodium channels in peripheral nerves [5,6]. In the mouse diaphragm, oxaliplatin induced multiple endplate potentials following a single stimulus. It also increased spontaneous endplate potential frequency that a voltage-gated sodium channel blocker prevented. Carbamazepine, which slows sodium channel recovery from inactivation, also substantially reduced the effects of oxaliplatin [6].

Oxaliplatin-associated chronic sensory neuropathy is similar to that of cisplatin. The development of neuropathy is cumulative and dose related [2]. Mean cumulative

Table 1. Common neurologic toxicities of frequently employed chemotherapies

Drug	Central nervous system	Peripheral nervous system
Cisplatin		Sensory neuropathy
Carboplatin		Sensory neuropathy
Oxaliplatin		Acute neuropathic syndrome
Paclitaxel		Sensory neuropathy
Docetaxel		Sensorimotor neuropathy
Vincristine		Sensory neuropathy
Ifosfamide	Encephalopathy	Sensorimotor and autonomic neuropathy
Asparginase	Stroke	
Fluorouracil	Encephalopathy, cerebellar dysfunction	
Methotrexate	Aseptic meningitis, myelopathy (intrathecal administration), stroke-like focal deficits, seizures, chronic encephalopathy	
Cytarabine	Encephalopathy, seizures, cerebellar dysfunction, aseptic meningitis, myelopathy (intrathecal)	

dose in symptomatic patients was 1787 mg in symptomatic patients compared with 1110 mg in asymptomatic patients [7]. Nerve conduction studies, which demonstrate decreased sensory nerve action potential amplitude with relatively preserved conduction velocities and motor responses, are distinct from those found in the acute neuropathic syndrome and closely resemble those found in cisplatin-induced chronic sensory neuropathy [3•,7]. A history of acute oxaliplatin-induced neuropathy did not predict a chronic neuropathy [7]. Paresthesias tend to improve over months following cessation of treatment, although nerve conduction studies remain abnormal [7].

In animal studies, oxaliplatin significantly reduced dorsal root ganglion volume but had no effect on total number of nerves. Oxalipatin, however, alters the size distribution of neurons within the dorsal root ganglion with significant reduction in average cell size. In addition there is a decrease in the number of large neurons and a corresponding increase in small neurons, suggesting that oxaliplatin exposure causes selective large neuron atrophy. Oxaliplatin does not affect small neurons. Changes in dorsal root ganglion correlate with findings on nerve conduction studies [8].

Several preventive interventions have been evaluated to prevent or treat oxaliplatin neuropathy. Most studies, however, included only a small number of patients, and large prospective studied have not been performed. In a retrospective series of 161 colon cancer patients treated with oxaliplatin, 96 received infusions of calcium gluconate and magnesium sulfate prior to and after oxaliplatin infusions. Neurotoxicity, both acute and chronic, was less frequent and less severe among those treated with calcium and magnesium. Treated patients that did develop a neuropathy had more rapid reversal of their symptoms following discontinuation of oxaliplatin. Furthermore, only 4% of the treated group withdrew from treatment secondary to neurotoxicity compared with 31% in the untreated group [9•]. Two separate studies evaluating the efficacy of carbamazepine administered with oxaliplatin reported conflicting results. Wilson et al. [4] did not identify any benefit, either clinically or on nerve conduction studies, when carbamazepine was given 5 days prior to and 2 days after oxaliplatin infusion beginning during the second cycle. Lersch et al. [10], however, reported a significant decrease in grade 3 or 4 neuropathy compared with historical control subjects when carbamazepine was administered continuously beginning 1 week prior to the first infusion. Methodologic differences between studies may account for the differences. Amifostine, administered intravenously or subcutaneously, has also been shown to reduce oxaliplatin-induced neuropathy [2,11].

Thalidomide

Thalidomide was first introduced into European markets in the 1950s as a sleep aid and antiemetic for pregnant women. It was withdrawn from the market soon thereafter when its teratogenic effects were discovered. It has re-emerged recently as an effective treatment for several dermatologic, gastrointestinal, and oncologic conditions. Peripheral neuropathy is now recognized as one of the most significant complications of this medication. The most common presentation is distal parasthesias and/or dystasias with or without sensory loss. Physical examination may be normal or show mild reduction in sensation in distal limbs. Strength is usually preserved although mild weakness may be present. Reflexes, particularly ankle jerks, may be depressed or absent. Symptoms are progressive, usually beginning in distal lower limbs but extending proximally and into upper extremities. Symptoms can be quite disabling and often necessitate discontinuation of the drug despite disease control. Onset is usually 1 year after initiating thalidomide. On nerve conduction studies, reduction in sensory nerve action potential amplitude

with relative preservation of conduction velocities and compound motor action potentials consistent with a sensory axonal neuropathy are typical findings [12].

Alternatively, thalidomide may cause a neuronopathy. Such patients present with early involvement of all four limbs. Nerve conduction studies show isolated reduction in the amplitude of sensory nerve action potentials in all limbs (including sural nerves) and somatosensory evoked potentials show prolonged spinal and cortical latencies. T2 hyperintense, non–mass-like, non-enhancing lesions may be seen in the posterior columns of the spinal cord on MRI. Such cases may present with less cumulative thalidomide exposure [12,13].

Conflicting results regarding the relationship of thalidomide dosage and incidence of neuropathy exist. Although some studies found a relationship between cumulative dosage and occurrence of neuropathy [14,15•], others failed to do so [16–18]. Cavaletti et al. [15•] noted a dose relationship beginning at cumulative doses of 20 g. In several studies that failed to identify a dose relationship, median doses were below this level [16,18]. Alternatively, risk of neuropathy may be related to daily dose although this has been reported less frequently [18]. Neuropathic symptoms may improve with discontinuation of thalidomide [12,14].

A neuropathy present in patients treated with thalidomide may be a complication of the underlying condition (eg, multiple myeloma or lupus erythematosus) or previous or concurrent treatments (eg, vincristine). Several series, however, report normal nerve conduction studies prior to initiation of thalidomide. Furthermore, the pattern of neuropathy is distinct from those typical of these conditions. Risk factors for neuropathy have not been elucidated and most studies failed to find a correlation between age and indication for thalidomide and occurrence of neuropathy [16–18]. Preliminary clinical data suggest that thalidomide analogues lenalidomide and CC-4047 are more potent and have a better toxicity profile, including less neuropathy.

Neuroprotection

Amifostine

Amifostine, a cysteamine analog, has been used as a cytoprotective agent to abrogate chemotherapy-induced toxicities, including neuropathy. Amifostine, a prodrug activated by alkaline phosphotases that are more abundant in normal tissue, may selectively protect normal tissue without reducing antitumor activity. It may be administered intravenously or subcutaneously, the latter possibly being better tolerated [11,19]. Possible mechanisms of action include scavenging of free radicals, repair of DNA-DNA cross-links induced by alkylating drugs, and removal of platinum DNA adducts. In vitro studies demonstrated that amifostine protects against paclitaxel- and cisplatin-induced neurotoxicity in nerve growth factor–induced neurite assays [20]. Amifostine reduced ototoxicty in guinea pigs treated with cisplatin [21]. Clinical data, limited by study methodology, has been conflicting. In a recent study, patients with ovarian cancer treated with paclitaxel and carboplatin, with or without epirubicin, were randomized to pretreatment with amifostine or placebo. A significant protective effect of amifostine was observed for two-point discrimination, vibration perception and disappearance threshold, and tendon reflex activity. Toxicities according to the National Cancer Institute's common toxicity criteria showed improved sensory neuropathy but a worsening in terms of nausea and vomiting [22]. Among ovarian cancer patients treated with paclitaxel and carboplatin, amifostine significantly reduced grade III or IV neuropathy from 7.2% to 3.7% [23]. On the contrary, in patients treated with high-dose paclitaxel, no significant beneficial effect of amifostine on nerve conduction studies or quantitative sensory analysis was demonstrated [24]. Amifostine increased toxicity and did not prevent neurotoxicty in patients with metatstaic melanoma treated with cisplatin [25]. Similarly, amifostine was ineffective when given with combined paclitaxel/cisplatin regimens [26,27]. Amifostine, administered subcutaneously or intravenously, may be effective in patients treated with oxaliplatin although data are limited [11,28]. As the postulated mechanism of action of amifostine is at the DNA level, it is unsurprising that the neuroprotective effect is unequivocal in patients treated with paclitaxel (neuropathy thought to be caused by impaired microtubule assembly) [24]. This may account for some of the negative studies reported thus far. Additional studies incorporating clinical and electrophysiologic endpoints are required to determine the utility of this agent.

Neurotrophins and cytokines

Through incompletely understood mechanisms, nerve growth factor (NGF), a member of the neurotrophin family of neurotrophic factors, plays a role in differentiation, maturation, and survival of neurons within the peripheral nervous system. It has been suggested that deficient production and/or impaired uptake and transport of NGF may contribute to the development of neuropathies, including those caused by chemotherapies. Circulating levels of NGF are decreased in humans [29,30] and animals [31] treated with platinum agents and paclitaxel. Circulating levels of NGF may correlate with nerve conduction velocities in the tail nerve of rats [31] and with neurologic dysfunction in humans [29,30]. Exogenous administration of NGF may be neuroprotective in platinum-, paclitaxel-, and vincristine-treated animals [32,33]. When co-administered with cisplatin, recombinant NGF partially prevented the typical morphologic changes in the dorsal root ganglion and peripheral nerves typical of platinum neurotoxicity and nerve conduction velocities were preserved [33]. Platinum agents

may decrease production of NGF in the peripheral tissues [32]. In addition, both cisplatin and taxanes may interfere with retrograde axonal transport, an important mechanism by which NGF exerts its effect in neurons. Exogenous administration of NGF to humans may be limited by local and systemic side effects. Different approaches, including the use of NGF-modulating drugs or gene transfer strategies, may be an alternate approach. Similarly, leukemia inhibitory factor (LIF), a member of the gp130 group of cytokines, has been shown in several models of nerve injury to exert a neuroprotective effect. In vivo preclinical studies have shown that recombinant LIF may prevent nerve injury in animals treated with paclitaxel and platinum agents [34]. Importantly, it did not interfere with the antitumor activity of the drugs [34]. In a randomized, placebo-controlled trial, however, it was ineffective in preventing, delaying, or diminishing the magnitude of neuropathy in patients treated with carboplatin and paclitaxel [35].

Acetyl-L-carnitine

Acetyl-L-carnitine (ALC), a natural compound synthesized in the brain, liver, and kidneys, is neuroprotective in different experimental paradigms [36]. When administered to rats prior to and concomitantly with cisplatin or paclitaxel, sensory nerve conduction velocities were less significantly affected compared with when these chemotherapies were administered alone. Also, NGF levels were relatively preserved and their effects of gene expression potentiated. ALC reduced neurite damage in paclitaxel- and cisplatin-treated cells and morphologically there was less evidence of neuronal injury. ALC did not affect the antitumor activity of these agents [36]. ALC increases histone acetylation by donating acetyl groups to histones, thereby modulating gene expression. Presumably, genes involved in tissue repair are affected. Two small studies have demonstrated clinical and elctrophysiologic benefit of ALC in cancer patients with neuropathy treated with cisplatin and/or paclitaxel [37,38]. Larger studies are needed to evaluate this compound.

Encephalopathy

Methotrexate

Methotrexate is used in a variety of settings, including treatment and prophylaxis of cerebrospinal fluid (CSF) dissemination in adult and pediatric malignancies. Methotrexate acts by inhibiting dihydrofolate reductase, thereby preventing the conversion of folate to its reduced metabolite, which acts as a methyl donor in several intracellular reactions.

Acutely, intrathecal methotrexate may cause aseptic meningitis characterized by headache, neck pain, nausea and vomiting, fever, and photophobia. Symptoms can usually be prevented or treated with corticosteroids and generally do not result in significant disability and hospitalization is rare.

Subacute methotrexate neurotoxicity is best characterized in pediatric patients receiving intrathecal chemotherapy for acute lymphocytic leukemia (ALL). It has also been reported in adults and in patients treated with high-dose intravenous methotrexate [39–43]. Subacute toxicity is characterized by acute, stroke-like onset of focal neurologic deficits and seizures usually occurring within 2 weeks of a treatment [41,44]. Patients may also develop a myelopathy characterized by limb weakness, back pain, and bladder dysfunction [42,45]. Symptoms are usually self limited and resolve within 1 week. Symptoms usually do not recur with re-treatment [41,44]. Rarely, rapid progressive deterioration after methotrexate treatment culminating in patient death may occur [39,42,46]. Acutely, MRI may show focal, bilateral, asymmetric restricted diffusion defects within the hemispheric subcortical white matter most often within the centrum semiovale. The lesions are hypointense on apparent diffusion coefficient maps. On follow-up imaging, a focal T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity may replace the diffusion defect even when clinical recovery is complete [43,44,47,48]. The lesions usually do not enhance and may not localize to the clinical deficit [44]. CSF compartmentalization secondary to fluid flow obstructions is common in patients with leptomeningeal metastases and may increase the risk of toxicity by trapping methotrexate, thereby exposing adjacent brain to toxic concentrations of drug [39]. Such obstructions may not be detected on CT or MRI, and nuclear flow studies may be necessary. Alternatively, chemotherapy may backflow along the ventricular catheter track, consequently damaging the surrounding white matter [49].

Chronically, high-dose intravenous methotrexate has been associated with the development of diffuse subcortical T2/FLAIR hyperintensities on MRI. Focal enhancement is occasionally present and may represent necrosis [46,50]. This finding may be associated with a worse prognosis. Surrounding mass effect is minimal and, in fact, cerebral atrophy may be present. The abnormalities, commonly referred to as leukoencephalopathy, may be detected in asymptomatic patients during treatment. Lesions usually regress in the months that follow treatment, although residual hyperintensities may remain on T2/FLAIR images [51,52•]. The incidence and extent of the lesions may increase with increasing drug exposure (ie, methotrexate dosage and number of treatments) [51]. On magnetic resonance spectroscopy, N-acetyl aspartate/choline and choline/creatine ratios transiently decrease and increase, respectively, in children during the 2 weeks following completion of treatment. Spectroscopic changes were detected in patients with and without white matter changes and no correlation with cumulative methotrexate dose was detected [51]. The significance of radiographic abnormalities remains unclear. Historically,

the association of leukoencephalopathy and neurocognitive disturbances has been indeterminate. Child survivors of systemic ALL treated with methotrexate often suffer with intellectual impairment and learning disabilities [53–55]. Adults, most often treated with high-dose intravenous methotrexate for primary central nervous system lymphoma, develop a syndrome closely resembling normal pressure hydrocephalus characterized by disturbances of memory, attention, and gait, and urinary incontinence. Younger and older age may increase risk of neurologic toxicity among pediatric and adult patients, respectively [56]. All patients, however, are at significant risk [56]. Cognitive deficits may be selective and global functioning may not be significantly impacted. School placement of treated children is similar to healthy siblings, and adult patients are often able to return to work, although occasionally at a lower capacity [54,56,57•]. Although an association exists between methotrexate and cognitive impairment, a causative relationship is difficult to establish. Usually patients are treated with other therapies concomitantly, including alternative neurotoxic chemotherapies and radiotherapy. In recent years, radiotherapy has been deferred in both pediatric and adult protocols in lieu of chemotherapy. Consequently, methotrexate appears to be better tolerated with fewer cognitive side effects [54,57•,58•,59–62]. Although methotrexate may cause a radiographic leukoencephalopathy, most recent studies fail to correlate radiographic findings and the results of cognitive testing [53,54,58•,63]. One recent study of long-term, disease-free survivors of primary central nervous system lymphoma, however, found that patients with more extensive white matter disease did worse in selective cognitive domains than those with less extensive involvement [57•].

The mechanism of methotrexate-induced toxicity remains unknown. 5-methyltetrahydrofolate, a reduced metabolite of folate that is depleted in the presence of methotrexate, is required for conversion of homocysteine to methionine. It has been suggested that folate and homocysteine levels may be a determinant of methotrexate toxicity. Homocysteine is toxic to vascular endothelium and its metabolites may activate N-methyl-D-aspartate (NMDA) receptors. Plasma and CSF levels of homocysteine and its metabolites may increase transiently following treatment with methotrexate [40,64]. In a recent case report, considerable acute toxicity occurred during treatment with high-dose methotrexate therapy in a patient with significantly depressed and elevated folate and homocysteine levels, respectively. Subsequent, identical cycles of treatment associated with more appropriate levels were uncomplicated [65]. Patients with homozygous mutations of methylenetetrahydroxyfolate reductase, an enzyme pivotal in folate metabolism, may be at higher risk of toxicity [66]. The presence of polymorphisms that influence methionine metabolism may increase the risk of white matter injury [67•]. In a longitudinal study, however, neither CSF nor serum levels of homocysteine correlated with occurrence of acute neurotoxicty [64]. Alternatively, methotrexate toxicity may result from increased adenosine observed with methotrexate. Aminophylline, an adenosine antagonist, has been reported to reverse neurologic toxicity [68]. Dextromethorphan, an NMDA antagonist, has also been reported to reverse methotrexate-associated neurotoxicity [40]. Nonetheless, no treatment has been proven to prevent or correct neurotoxicty, and most therapeutic reports are anecdotal, with a treatment effect difficult to separate from spontaneous resolution of symptoms.

Ifosfamide

Ifosfamide, an alkylating agent and cyclophosphamide isomer, is active against a broad range of tumors. Ifosfamide and its metabolites readily cross the blood-brain barrier and neurologic toxicity is common, occurring in 10% to 50% of exposed patients. It is a prodrug that undergoes p450-dependent metabolism into an active metabolite, ifosfamide mustard. In addition, it is deactivated into chloroethyl intermediates and ultimately chloroacetaldehyde (CA) [69].

The most common clinical presentation of the neurotoxic effects of ifosfamide is an encephalopathy, manifesting as altered sensorium, ranging from mild confusion to coma. Psychosis, hallucinations, status epilepticus (convulsive and non-convulsive), and cerebellar and extrapyramidal dysfunction have been reported. Onset is usually within 24 hours of exposure, although delayed onset has been reported. Symptoms are generally self-limited and resolve spontaneously within hours to days of ifosfamide discontinuation. Rarely, the encephalopathy may be fatal. The encephalopathy is more common on initial exposures (usually occurring during the first or second cycle) [70]. Symptoms are usually less frequent and intense on subsequent treatments. Risk factors have yet to be definitively determined. Age, renal and hepatic dysfunction, low albumin, and pelvic disease have inconsistently been identified as risk factors [70,71]. The presence of polymorphisms of genes encoding glutathione-s-transferases, enzymes responsible for activation and detoxification of ifosfamide metabolites, failed to correlate with the occurrence of neurotoxicity [72]. Oral or rapid intravenous administration may increase the risk of encephalopathy compared with continuous intravenous infusion, suggesting a relationship with peak serum concentrations.

Several possible mechanisms of neurotoxicity have been suggested, most involving metabolites of ifosfamide. CA is structurally related to chloral hydrate, a known hypnotic, and acetaldehyde, a neurotoxic metabolite of ethanol. CA has also been shown to deplete intracellular glutathione in in vitro and in vivo models. Chloroethylamine undergoes a series of reactions eventually forming thialysine ketimine. This sulphur-containing compound is a potent inhibitor of flavoproteins, the mitochondrial

respiratory chain, and fatty acid metabolism. Thialysine ketamine is also an inhibitor of NADH oxidation. As a consequence, hepatic gluconeogeneis is interrupted and the oxidation of aldehydes, including CA, is impaired. Ultimately, these metabolic derangements lead to accumulation of toxic intermediates, decreased adenosine triphosphate (ATP) production, and impairments of global neurologic function [69,71].

The management of ifosfamide encephalopathy is primarily supportive. Awareness of this complication and reassurance of the patient and family are crucial. Clinical or electrographic seizure activity should be treated appropriately. Antipsychotics may be used to treat patients with psychosis or hallucinations. Methylene blue (MB) has emerged as an agent to treat and prevent the encephalopathy. MB may act as a substitute for flavoproteins by acting as an electron acceptor, thereby restoring electron transfer within the mitochondria, fatty acid oxidation, and ATP synthesis. It may also lead to NADH re-oxidation. MB may inhibit monoamine oxidase, thereby preventing the formation of CA (another mechanism by which this metabolite is formed from ifosfamide) [73]. The clinical utility of MB remains unclear. Small case series suggest that treatment with MB may shorten the course of the encephalopathy [73–75]. It is, however, difficult to separate the spontaneous recovery of the syndrome from a treatment effect [70,74]. In addition, the impact of MB on the cytotoxic activity of ifosfamide is uncertain. Thus, routine use of MB is not indicated. In the setting of severe toxicity, however, treatment with MB is indicated. Alternatively, MB is advocated by some as a prophylactic measure when re-treating patients who previously experienced neurotoxicity. Anecdotally, this approach has been reported to prevent recurrent toxicity [74,76].

Cytosine arabinoside (cytarabine)

Cytarabine is a pyrimidine analog that is incorporated into DNA during DNA synthesis, forcing premature termination of DNA elongation and, ultimately, DNA strand breaks. Neurologic toxicity is a well-recognized complication of this agent when administered intravenously. Most often it has been associated with a cerebellar syndrome of gait and limb ataxia that occurs within hours of treatment. Altered mental status and seizures have also been reported. Symptoms usually resolve spontaneously with cessation of treatment. High doses (> 1 g/m^2), advanced age (> 55 years), and renal dysfunction are thought to increase the risk of this complication. Patients may be re-treated, albeit at a lower dose.

The mechanism of injury is unclear. Pathologic studies have shown a loss of Purkinje cells within the cerebellum, and cytarabine induces apoptotic death of cultured neurons. Cytarabine may disrupt the balance of cyclin-dependent kinases resulting in cell death [77]. Cytarabine may induce the formation of reactive oxygen species, which cause DNA strand breaks and, ultimately, p53-dependent apoptosis [78]. Cytarabine may induce astrocytes to release soluble factors that increase the susceptibility of neurons to glutamate [79]

Cytarabine can also be administered intrathecally. The recent development of a sustained-release formulation permits less frequent injections than the standard formulation or methotrexate. Intrathecal cytarabine is associated with similar acute toxicity and complications as methotrexate. It may induce aseptic meningitis and, rarely, seizures and a myeloencephalopathy.

"Chemo Brain"

Cognitive impairment in the absence of direct involvement of the central nervous system has been demonstrated in cross-sectional studies of women who have received adjuvant chemotherapy for breast cancer [80–83,84••]. The incidence has varied widely between studies, probably as the result of study design. The data, however, have several limitations. Most studies are cross-sectional with evaluations performed at variable times during or after the completion of chemotherapy. Thus, it is impossible to qualify the extent of cognitive change within an individual, yet 35% of women with breast cancer exhibited cognitive impairment prior to any treatment [84••]. Instead, control groups were employed, the selection of which has differed between studies. Control subjects have included patients with similar disease of lesser stage not treated with chemotherapy, normative data, healthy control subjects, or patient-selected controls. Cognitive batteries and definitions of impairment have also varied, and nonuniform chemotherapeutic regimens were used. Sample sizes were small, limiting the analysis of the data. The impact of hormonal therapy, the use of which varied between studies, was not always factored into the analysis. Nonetheless, all studies found impairment in patients compared with control subjects. The level of impairment did not correlate with anxiety, depression, fatigue, or menopausal symptoms, all of which are possible confounders [80,81,83,84••]. These symptoms, however, did correlate with subjective complaints of cognitive impairment [81]. In turn, subjective complaints did not predict cognitive dysfunction on neurophsychiatric assessment [81,82]. Deficits may persist despite prolonged remission and treatment-free intervals [82]. Dose response is difficult to assess, although patients treated with high-dose regimens (with stem cell rescue) were 3.2 times more likely to be impaired compared with those treated with standard regimens (although the difference was not significant) [81]. More cycles of chemotherapy were associated with lower performance [82]. None of the studies found relationships between regimens administered and outcome, although subgroups were small.

In the only prospective longitudinal study performed to date, 33% of patients with breast cancer had cognitive dysfunction prior to chemotherapy. At short-term and long-term follow-up, mean test scores were stable.

However, 61% of patients experienced a decline in one or more aspects of cognitive functioning that was not related to mood, demographic characteristics, clinical features, or baseline impairment. The most common affected domains were attention, learning, and processing speed, which are consistent with disruption of frontal network systems. Overall declines were subtle although they were associated with a higher incidence of functional loss, including the ability to work. One-half of patients experiencing cognitive dysfunction improved at long-term follow-up. The authors suggest that approximately 46% of patients would not have been classified as having experienced cognitive decline based on their post-chemotherapy evaluations had they not undergone baseline cognitive assessment [84••].

The pathogenesis of cognitive impairment is unclear. Methotrexate and 5-fluorouracil, both neurotoxins, were incorporated into many of the regimens, suggesting a direct neurotoxic effect. Alternatively, cytokines, paraneoplasia, and microvasculopathy may cause cognitive impairment. These factors have not been analyzed. Asymmetry of alpha rhythm was found in a greater proportion of breast cancer patients treated with high-dose chemotherapy than patients treated with standard-dose or control subjects [85]. Otherwise, functional or metabolic imaging has not been thoroughly investigated in this condition.

The relationship between estrogen and cognitive performance has generated a significant amount of research but the impact of hormonal manipulation remains inconclusive. This dilemma is relevant among breast oncologists who frequently employ hormonal therapies including tamoxifen and aromatase inhibitors. Cytotoxic chemotherapies may also induce menopause, thereby depriving women of natural estrogens [83]. Clinical studies thus far failed to demonstrate a relationship between menopausal symptoms and tamoxifen usage and cognition, although subgroups were small [83]. The impact of aramotase inhibitors on cognition has not been explored in clinical trials [86]. Nonetheless, given the role estrogen may play in cognition, further attention to hormonal factors is essential.

Conclusions

It is imperative that our treatments do not diminish quality of life as the overall survival of patients with cancer improves. A better understanding of neurotoxicity will lead to novel agents with diminished neurotoxic potential as well as therapies to reverse or prevent injury. For now we must educate our patients and continue to strive to understand the risk factors and mechanism of injury so that we may better serve those for whom we care.

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