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CISPLATIN-BASED THERAPY: A NEUROLOGICAL AND NEUROPSYCHOLOGICAL REVIEW

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SUMMARY

The present paper reviews research in the area of the broad-spectrum chemotherapeutic agent cisplatin (*cis*-diamminedichloro-platinum II) and examines the implications for clinical neuropsychology arising from the neurological disruption associated with cisplatin-based therapy. The paper begins with a brief review of cisplatin treatment in terms other than survival alone, and examines the side-effects and the potential central nervous system (CNS) dysfunction in terms of neurological symptoms and concomitant implications for neuropsychology. Two main implications for clinical neuropsychology arising from cisplatin therapy are identified. First, cisplatin therapy impacts upon the psychological well-being of the patient, particularly during and in the months following treatment. It is suggested that during this time, a primary role for neuropsychology is to focus upon the monitoring and the active enhancement of the patient's social, psychological and spiritual resources. Second, with regard to neurocognitive changes, the review suggests that (1) neurocognitive assessment may not yield stable results within 8 months following treatment and (2) while perceptual, memory, attentional and executive dysfunction may be predicted following cisplatin treatment, little systematic research has been carried out to investigate such a possibility. Future research might profitably address this issue and also specifically examine the effects of low dosage cisplatin-based therapy and the effects of recently developed neuroprotective agents. Finally, there is some evidence to suggest that women may be more susceptible to neurotoxicity during cisplatin therapy, but no gender-related cognitive effects are reported in the cisplatin literature. Future research could usefully investigate gender differences in association with cisplatin chemotherapy. Copyright © 2000 John Wiley & Sons, Ltd.

INTRODUCTION

With the development and advancement of our understanding of chemotherapeutic treatment agents there has been a corresponding increase in the survival rates of cancer patients. However, there appears to be limited systematic research on the psychological and neuropsychological sequelae, which accompany potential and real neurological dysfunction in cancer-surviving populations. The present paper begins by reviewing research on the neurotoxic effects of one broad-spectrum chemotherapeutic agent—cisplatin (*cis*-diamminedichloro-platinum II)—and moves to examine current evidence regarding the outcome of treatment in terms other than survival alone. The present paper focuses specifically on the implications for clinical neuropsychology arising from the possible neurological disruption associated with cisplatin-based therapy.

CISPLATIN: HISTORY AND BACKGROUND

Among the first to report on the importance of platinum complexes for cancer treatment were Rosenberg *et al.* (1965, 1969) and Wallace and Higby (1974). Undoubtedly, the most dramatic effect of the drug has been the long-term survival of patients presenting with advanced testicular cancer (Rosenberg, 1985; Cersosimo, 1989; Kelland, 1993). However, cisplatin has also shown

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significant anti-neoplastic activity against urologic, ovarian, head, neck and small cell lung cancer (Holleran and DeGregorio, 1988; Macdonald, 1991; Tuxen and Hansen, 1994).

Cisplatin is usually combined with other cytotoxic agents: etoposide, bleomycin and (now less commonly) vinblastine (Berger *et al.*, 1995; Culine and Droz, 1996). Such combinations have been shown to be effective in increasing remission rates and reducing side-effects in the majority of patients with germ-cell cancer (De Koning *et al.*, 1987; Hansen, 1992; Bassetto *et al.*, 1995; Gerl *et al.*, 1996). A full discussion of the various neuroprotective drug combinations that are currently being investigated is beyond the scope of the present paper and the reader is thus referred to Kelly *et al.* (1992), Lewis (1994), Alberts and Noel (1995) and Van der Wall *et al.* (1995) for detailed reviews. It is sufficient to note that the combination of cisplatin, etoposide and bleomycin is now considered the standard cisplatin-based therapy and this combination is the primary focus of the present paper. Remission rates of 83%, with 5-year long-term survival of 65%, have now been reported for germ-cell cancers (Bassetto *et al.*, 1995) and survival for this group is now in the 93–100% range, independent of stage at diagnosis (Culine *et al.*, 1996; Kelty *et al.*, 1996).

SIDE EFFECTS OF CISPLATIN-BASED THERAPY

Many studies have reported that cisplatin has neurotoxic effects upon the peripheral nervous system (PNS) (e.g. Roelofs *et al.*, 1984; Mollman, 1990) and the central nervous system (CNS) (e.g. Berman and Mann, 1980; Walther *et al.*, 1987). The most commonly observed side-effects include neurotoxicity, emesis, nephrotoxicity, ototoxicity and moderate myelosuppression (El-Shazly *et al.*, 1989; Macdonald, 1991; Hussain *et al.*, 1993; Kelland, 1993; Tuxen and Hansen, 1994; Dominguez-Ortega *et al.*, 1996). More rare side-effects include ophthalmological effects, seizures and autonomic neuropathy (Cattaneo *et al.*, 1988; Cersosimo, 1989; Macdonald, 1991). These groupings of side-effects will be briefly considered in terms of neurological and neuropsychological implications for assessment, treatment and quality of life for the patient.

Neurotoxicity

Cisplatin neurotoxicity was first reported in the 1970s (Kedar *et al.*, 1978; Von Hoff *et al.*, 1979), and one consistent finding has been that the incidence of neurotoxicity increases with the cumulative dose. While many of the neurotoxic effects associated with intravenous administration diminish after cessation of therapy, recovery is not always complete and some cases take months to years for resolution (Hansen, 1992). In fact, worsening of symptoms over the months after cessation of treatment has been documented (Grunberg *et al.*, 1989); however, there appears to be large individual differences in long-term neurotoxic effects (Cavaletti *et al.*, 1994). For example, Pirovano *et al.* (1992) found the clinical picture remained unchanged for 2–3 months but showed a tendency to recovery within 6–8 months. Clearly, the assessment of neuropsychological functioning will yield varying results as a function of time since cessation of chemotherapy; this issue will be addressed more fully below.

Emesis (nausea and vomiting)

While emesis can be delayed for several days after chemotherapy, it is experienced by almost every patient and does not respond well to conventional anti-emetics (Rosenberg, 1985; Nolte, 1993). Adverse experience of emesis in the acute phase can lead to a conditioned anticipatory nausea and vomiting, which may be triggered by anything associated with treatment (Blijham, 1993; Gralla *et al.*, 1996; Hesketh, 1996; Verweij *et al.*, 1996; Davey and Biederman, 1998). The incidence and severity of delayed emesis is influenced by the dose of cisplatin and degree of emesis experienced in the acute phase (Hesketh, 1996; Roila, 1996). Those aged over 50 years and of the female gender also have an increased risk of emesis (Roila, 1996).

Metoclopramide (a serotonin antagonist) plus dexamethasone (an adrenal corticosteroid) is an effective antiemetic treatment (Gralla *et al.*, 1996) but a regimen of ondansetron plus dexamethasone (Ossi *et al.*, 1996; Roila, 1996) or conjoint granisetron, dexamethasone and prochlorperazine (Matsui *et al.*, 1996) have shown the greatest efficacy in control of vomiting over repeated courses of chemotherapy. Dominguez-Ortega *et al.* (1996) suggest that administration of cisplatin

and anti-emetic medication during sleep also reduces emesis. However, the drugs used to treat emesis are not without their own side-effects (see Macdonald, 1991, Gralla *et al*., 1996 and Verweij *et al*., 1996 for discussion) and, as is considered below, this in turn has implications for neuropsychological assessment and treatment.

Nephrotoxicity

Nephrotoxicity is one of the primary dose-limiting side-effects of cisplatin (El-Shazly *et al*., 1989; Leibbrandt *et al*., 1995; McKeage, 1995). However, effective prophylactic treatments for nephrotoxicity have recently emerged and are being developed (Srivastava *et al*., 1995; Gaedeke *et al*., 1996). Nephrotoxicity can be considerably reduced by the maintenance of adequate hydration, the use of saline or mannitol diuresis, and the use of substances like WR-2721 (Hayes *et al*., 1977; Merrin, 1977; Mollman, 1990; Hamers *et al*., 1991; Blijham, 1993; McKeage, 1995; Gaedeke *et al*., 1996). In general, there appears to be limited implications for neuropsychology arising from problems owing to nephrotoxicity.

Peripheral neuropathy

Tuxen and Hansen (1994) calculated the incidence of cisplatin-associated neuropathy as an average of 57% of patients. However, these authors noted that this figure may be misleading (see also Cersosimo, 1989) as no account was taken of differences in patient populations, cumulative disease prior to or concurrent with therapy, or the introduction of other potential neurotoxins, such as vinca-alkaloids, etoposide or hexamethylmelamine, concurrently with or prior to cisplatin therapy. The earliest detected neuropathy appears after a total of 300 mg/m^2, and almost all patients had evidence of neuropathy following the administration of 500–600 mg/m^2 (Roelofs *et al*., 1984; also see review by Cersosimo, 1989).

The features of sensory peripheral neuropathy are consistent across studies and suggest damage to large myelinated sensory fibres, taking the form of progressive symmetrical sensory neuropathy, with initial paresthesias and more severe sensory ataxia (e.g. Thompson *et al*., 1984). Reviews by Cersosimo (1989), Mollman (1990) and Tuxen and Hansen (1994) described specific symptoms as follows. Patients first report numbness, tingling or paresthesias. The sensations usually begin in the hands and/or the feet and spread proximally. Patients exhibit a decreased vibratory sensation and continued cisplatin therapy may lead to a decrease in proprioception for the affected areas and diminished or absent deep tendon reflexes. Elderson *et al*. (1989) reported that vibration perception threshold returned to normal within 8 months post-cessation of treatment. Diminution of pain and temperature sensation is rare (Elderson *et al*., 1989; Pirovano *et al*., 1992).

Patients may suffer impairment of fine motor coordination, and in severe cases gait disturbances may occur, but these are generally related to sensory loss (Cersosimo, 1989; Pirovano *et al*., 1992). Most studies have found no significant changes in motor parameters and that cisplatin does not appear to affect the motor system (Cavaletti *et al*., 1991; Tuxen and Hansen, 1994). The reverse is true of studies of sensory parameters, where disturbance is found involving sensory nerves with the dorsal root ganglia being the primary vulnerable neural structure (e.g. De Koning *et al*., 1987; Mollman, 1990; Cavaletti *et al*., 1991; Potkul *et al*., 1991; Gregg *et al*., 1992). Results of other studies have confirmed sensory root ganglia disruption with secondary axonal degeneration (e.g. Hansen *et al*., 1989; Gregg *et al*., 1992). Axonal degeneration in the medulla oblongata has also been implicated in neuropathy (Hansen *et al*., 1989; Hansen, 1992). Lhermitte's sign (sensation of a sudden electrical impulse, travelling along the spine to the legs and feet on flexion of the neck) has also been observed upon completion of a 350 mg/m^2 cisplatin course (Walther *et al*., 1987; Inbar *et al*., 1992).

It is apparent that any neuropsychological assessment of higher-order cognitive functions needs to make allowances for possible lower-order sensory dysfunction. Cognitive tests are dependent on adequate fine motor activity and efficient somato-sensory functioning for their validity and reliability and, without these, such tests will likely yield spurious results. This may prove to be a more serious problem if neurocognitive assessment is attempted within only a few months of cisplatin treatment.

Ototoxicity

High frequency hearing loss constitutes an irreversible side-effect in an estimated 39% of

patients, and hearing loss in the speech range has also been documented in children treated with cisplatin for brain tumours (Maiese *et al.*, 1992; Ilveskoski *et al.*, 1996). Hansen *et al.* (1989) found that, at long-term follow-up (in remission for more than 3.5 years), 88% of patients treated with an average cumulative dose of 583 mg/m^2 cisplatin exhibited a prolonged central conduction time from the organ of Corti to the midbrain. Cisplatin-induced ototoxicity possibly arises either from the antioxidant status of the cochlea being impaired (McKeage, 1995; Ravi *et al.*, 1995) or, less likely, from an impaired blood supply to the brain caused by a treatment-induced vasospastic reaction (Hansen *et al.*, 1989). Again, there are clear psychological and neuropsychological implications arising from ototoxicity in that auditory dysfunction could have an impact on patient assessment and therapy and also on the evaluation of quality of life factors.

Ophthalmological dysfunction and seizures

Ophthalmological effects range from decreased visual acuity to cases of transient blindness (Berman and Mann, 1980; De Koning *et al.*, 1987; Cattaneo *et al.*, 1988). Cattaneo *et al.* (1988) found delays in the latency of visual-evoked potentials consistent with pathology of the anterior visual pathways (optic nerve, chiasm and optic tract) and occipital lobe dysfunction (see also De Koning *et al.*, 1987; Maiese *et al.*, 1992).

Cersosimo's (1989) review of research into transient blindness indicates that such patients also suffer grand mal seizures several hours after intravenous cisplatin infusion and exhibit spontaneous recovery within 4 days (see also Berman and Mann, 1980; De Koning *et al.*, 1987). Thus, transient blindness and seizures appear to be associated with abnormally high levels of platinum and may be a function of heavy metal (platinum) intoxication of either, or both, the anterior visual pathways and the posterior cortical regions. In light of this evidence, it may be predicted that, even at low dose levels, visual perceptual difficulties will be encountered post-cisplatin treatment. Such was reported by Kaasa *et al.* (1988) who found that, amongst a range of tests, a visual retention test was the only one to show significant increases in performance errors at 14 weeks post-cisplatin therapy.

Autonomic neuropathy

Autonomic nervous system neuropathy presents as parasympathetic damage and Raynaud's phenomenon (intermittent spasm of the digital arteries precipitated by cold or stress), which is possibly explained by hyper-reactivity of the central sympathetic nervous system (Hansen, 1992; Berger *et al.*, 1995; Fossa *et al.*, 1995). Hansen (1990), in a retrospective study of 28 patients, found indications of parasympathetic nerve damage in 10 patients. The only complaint that was potentially related to autonomic dysfunction was impotence, which was observed in three patients. In this regard, there would appear to be a general need for more research into the impact of cisplatin treatment on sexual functioning and concomitant quality of life factors (Siimes *et al.*, 1993; Van Basten *et al.*, 1997).

CNS neuropathy

Chemotherapeutic agents, including cisplatin, are generally regarded as being largely excluded from passing through the blood–brain barrier, and thus the findings that cisplatin causes CNS neuropathy have been controversial (Neuwelt *et al.*, 1983). Cisplatin has shown poor penetration of the CNS after intravenous infusion (Thompson *et al.*, 1984). Gregg *et al.* (1992) assessed the neural tissue platinum levels of patients at post-mortem and found that cisplatin was effectively excluded from the frontal lobes by the blood–brain barrier. However, it is possible that the platinum levels in other cortical structures (e.g. occipital lobes) may have been higher, but these were not examined.

Pharmacokinetic studies of radioactive cisplatin infusion have suggested poor penetration in the CNS; however, results suggest that repeated high doses of cisplatin may lead to an accumulation of platinum in the CNS, resulting in central neurotoxicity (Cattaneo *et al.*, 1988; Kaasa *et al.*, 1988). Histopathological examination of cisplatin-treated rats by El-Shazly *et al.* (1989) revealed degenerative changes in CNS with focal areas of necrosis, neuronophagia, gliosis and parenchyma. Similarly, Olivi *et al.* (1993) reported non-specific vacuolar changes in the white matter, axonal shrinkage and neurofibrillar accumulations, while Clark *et al.* (1980) found demyelination and focally enlarged axons in the optic disk, the

retrolaminar optic nerve and the long tracts of the spinal cord (see also Thompson *et al.*, 1984; Walther, *et al.*, 1987). Frustaci *et al.* (1987), in a study of intra-arterial cisplatin, reported cranial nerve impairment (admittedly at a low incidence of 6.3%). The foregoing studies suggest that cisplatin causes damage to both the CNS and the PNS (see also Bonnem *et al.*, 1982, Neuwelt *et al.*, 1983 and Cavaletti *et al.*, 1992). There would appear to be sufficient evidence to suggest that cisplatin has the ability to cross the blood–brain barrier. This has important implications for the neurocognitive assessment and functioning of patients who have received cisplatin-based therapy.

NEUROPSYCHOLOGICAL ASSESSMENT AND COGNITIVE–BEHAVIOURAL FUNCTIONING

There are two main considerations regarding the implications for clinical neuropsychology arising from cisplatin therapy; one is the psychological impact of the side-effects of cisplatin and the other concerns the long-term cognitive and behavioural impact arising from possible CNS damage.

With regard to the former issue, emesis is the most distressing and anxiety-provoking symptom perceived by the patient undergoing cisplatin treatment (Carey and Burish, 1988; Hesketh, 1996). As Bloom *et al.* (1998) noted, the more physically intrusive the illness, the higher the risk for dysfunctional affective states, such as depression. For example, the prevalence of psychiatric disorders within patients undergoing cancer treatment has been estimated at 47%, with reactive depression and anxiety being the most common diagnoses among these patients (Derogatis *et al.*, 1983, as cited in Redd *et al.*, 1991; Payne *et al.*, 1997; Holland *et al.*, 1999). Other studies have reported depressive states in 40% of patients before the commencement of chemotherapy (10% with major depression), with a low to moderate decrease in self-reported depression over 6 months (Middelboe *et al.*, 1994) which resolves itself by 12 months post-treatment (List *et al.*, 1999). Bloom *et al.* (1998) argued that the degree of impact of the disease and the treatment on the patient's quality of life and well-being depends on that patient's psychological and social resources.

It is evident that the role of neuropsychology at the time of diagnosis and treatment is more to do with the general enhancement of a patient's social, psychological and spiritual resources and less with the evaluation and remediation of neurocognitive difficulties (Holland *et al.*, 1998). Such enhancement has been shown to be achievable with a variety of treatment packages. For example, Carey and Burish (1988) positively evaluated the treatment procedures based on hypnosis, relaxation training, systematic desensitization, attentional redirecting and biofeedback. Focus groups have also been found to be useful (Ferrel *et al.*, 1997), while counselling for positive coping styles has been found to be effective and has been shown to be associated with lower levels of anxiety and greater flexibility in dealing with the illness (Holland *et al.*, 1999).

With regard to the second consideration, it appears to be the case that subtle cognitive impairment remains a common and unrecognized problem in cancer patients (Redd *et al.*, 1991). There are few systematic neuropsychological studies into the acute or chronic effects of cisplatin. However, given the demonstrated neurotoxicity of this substance, its impact on the PNS and its ability to cross the blood–brain barrier, a disruption of neuropsychological functioning would be expected following cisplatin therapy (Kaasa *et al.*, 1988).

The neurotoxicity of cisplatin, while not fully understood, resembles the neurotoxicity caused by inorganic salts and other heavy metals (De Koning *et al.*, 1987; Gregg *et al.*, 1992). For example, both mercury and lead have been shown to cause similar neurotoxic symptomatology to that of cisplatin (e.g. peripheral neuropathy, hearing loss and retinal changes: Anderson, 1982; Weiss, 1983; Discalzi *et al.*, 1993; Boivin and Giordani, 1995; Hartman, 1995). Ronnback and Hansson (1992 as cited in Hartman, 1995) proposed that low doses of lead and mercury are neurotoxic to astroglial structures, and also damage glutamate transmission, leading to secondary decreases in other neurotransmitter systems. It may be suggested that cisplatin has similar effects.

Given this resemblance between the neurotoxicity of cisplatin and that of other heavy metals, one may speculate that cisplatin patients will show emotional lability (as with mercury toxicity; White *et al.*, 1990; Yeates and Mortensen, 1994; Echeverria *et al.*, 1995), personality changes (as with manganese exposure; White *et al.*, 1990;

Wennberg *et al.*, 1991), and reduced general cognitive affect (as with lead exposure; White *et al.*, 1990; Stiles and Bellinger, 1993). A post-cisplatin neuropsychological assessment would ideally include an evaluation of these personality and affective domains, particularly to track recovery during the first 12 months post-therapy (List *et al.*, 1999), to enable effective counselling and to assist in the implementation of psychological and behavioural treatment procedures (Carey and Burish, 1988; Holland *et al.*, 1999)

It has been found that, in general, the most frequently occurring cognitive change reported by those exposed to neurotoxins are deficits in visuoperceptual, psychomotor constructional skills, reaction time, verbal conceptualization, short-term memory, attention and executive processes (Kaasa *et al.*, 1988; Braun *et al.*, 1989; Hein *et al.*, 1990; White *et al.*, 1990; Morrow *et al.*, 1992). Deficits in these particular domains would be consistent with what is known of the neuroanatomical targets of neurotoxic agents, those being, in particular, the hippocampus and amygdala, the striatal and basal ganglia regions, and possibly the frontal lobes (White *et al.*, 1990; Wennberg *et al.*, 1991; Wennberg, 1994). Neurotoxins do not typically produce aphasias, agnosias or apraxias unless a cerebrovascular accident (Kelly *et al.*, 1992) or severe anoxia occurs secondary to exposure (White *et al.*, 1992). Kaasa *et al.*'s (1988) findings, mentioned earlier, are in agreement with this observation in that these authors report no significant deficits on either a verbal learning task or a visuo-motor task, although they did find significant differences on a visual perceptual and memory task. Overall, it may be concluded that following cisplatin treatment, in order to effectively track recovery and any residual deficits, neuropsychological assessment needs to be relatively wide ranging to detect potential disruption to a variety of neurocognitive and psychological functions.

Furthermore, however, the effects of morphological changes need to be considered when undertaking neuropsychological assessment. These changes include axonal degeneration in the visual system and the spinal cord. In particular, tests designed to assess higher-order functions would be influenced by degeneration of axons in the optic disk, the retrolaminar optic nerve and the long tracts of the spinal cord. The pattern of recovery from PNS damage arising from cisplatin toxicity indicates that, while some patients show reduction of symptoms following cessation of therapy, there is a tendency for symptoms to remain unstable for the first 2–3 months. This is followed by a recovery in most patients within the first 8 months following cessation of therapy (De Koning *et al.*, 1987; Elderson *et al.*, 1989; Pirovano *et al.*, 1992). As was mentioned earlier, cognitive tests are dependent on adequate lower-order functioning for their validity and reliability; thus, neurocognitive assessment attempted within 8 months of cisplatin treatment may not yield stable results and may be prone to error.

While Silberfarb (1983) asserted that sporadic reports of gross evidence of cognitive impairment have been found for almost all of the commonly used chemotherapeutic agents, a literature search (Medline and Psyclit, 1993–1999) revealed only limited research on neuropsychological assessment and chemotherapy, and all but three studied children only (Berg *et al.*, 1983; Johnston, 1985; Johnston *et al.*, 1986; Copeland *et al.*, 1988; Fletcher and Copeland, 1988; Kaasa *et al.*, 1988; Moore *et al.*, 1992; Brown and Madan-Swain, 1993; Butler and Copeland, 1993; Garcia *et al.*, 1993; Ciesielski and Knight, 1994; Fossen, 1995).

Paediatric studies have found children treated for cancer score significantly lower on standardized measures of intelligence and academic skills, with deficits in attention, memory, speed of processing and analytic functions. However, these studies generally include children who had some CNS disease and rarely control for medication effects (Redd *et al.*, 1991). Studies conducted on younger children (under 36 months of age) with malignant brain tumours found that cisplatin had no effect on the achievement of developmental milestones; however, there was limited follow-up (1 year) and most of the children already suffered developmental delays as a result of their primary disease (Duffner *et al.*, 1993).

One of the studies that did focus on adults was conducted by Wieneke and Dienst (1995). They found that of 28 females with breast cancer who had received chemotherapy (not cisplatin), 21 (75%) were moderately impaired on one or more of a range of neuropsychological tests. A noteworthy finding is that the time elapsed since the cessation of chemotherapy (ranging from 0.5 to 12 months) was not significantly related to the level of cognitive impairment, but the duration of the chemotherapy was significantly related to impairment. The study by Kaasa *et al.* (1988), discussed earlier, only examined three cognitive test

instruments (covering verbal learning, visuomotor and visuoperceptual functioning) and pre–post assessment was not conducted. Other noteworthy studies reported evidence of dementia in three cancer patients with possible chemotherapy aetiologies (Davis *et al*., 1987) and that the impact of cisplatin therapy was still evident 5 years after the cessation of chemotherapy (Hansen, 1992).

In summary, this review of children and adult studies suggests that chemotherapy, specifically cisplatin therapy, can produce CNS toxicity and, subsequently, can result in decreased cognitive functioning. However, the precise effects on many higher-order cognitive and behavioural functions remain largely unknown. Extrapolation from likely CNS damage would suggest that cognitive impairment and, more specifically, perceptual, executive and short-term memory impairment would be expected because of possible frontal, hippocampal and amygdala dysfunction.

FUTURE RESEARCH

A noteworthy finding is the lack of studies regarding the effects of cisplatin on cognitive and behavioural functioning. Lezak (1984) argued that 'neuropsychological assessment probably offers the most sensitive means of examining the effects of toxic exposure . . . and of understanding the complaints and psychosocial problems of persons exposed to these toxins' (p. 28). It also remains unclear the effects of low dosage levels, which may or may not induce clear higher-order deficits. Future research in this area could usefully focus on cognitive functioning, particularly short-term memory, attentional and executive processes.

There is some evidence to suggest that women may be more susceptible to neurotoxicity during high dose cisplatin therapy, but the results are far from conclusive (De Koning *et al*., 1987). While no gender effects in terms of CNS effects are reported in the cisplatin literature, the organization of the male and the female brain has been shown to be different, although the nature of these differences is still under debate (Berenbaum *et al*., 1995; Reite *et al*., 1995). Reduced levels of gonadal hormones have also been found to influence cognitive performance (Swerdloff *et al*., 1992). The activation caused by gonadal hormones facilitates performance on simple repetitive tasks and impedes performance on inhibition tasks (Broverman *et al*., 1964; Komnenich *et al*., 1978). This proposal has been supported by more recent research (Gordon and Lee, 1986; Christiansen and Knussmann, 1987; Nass, 1993). Gordon and Lee (1986) stated that elevated gonadotropin levels coincide with relatively superior performance on verbal skills and that reduced levels of these hormones are associated with the reverse cognitive profile, where visuospatial skills are superior. Future research could usefully investigate gender differences in association with cisplatin chemotherapy. However, care should be taken to ensure that similar levels of cisplatin are received by all subjects and that the same combination of chemotherapeutic agents are used, as a variability in these factors would reduce the validity of higher-order neurocognitive comparisons.

Finally, the prevention of cisplatin neurotoxicity is now becoming a major focus of research, with substances such as nerve growth factor and amifostine showing promise (see Alberts and Noel, 1995, for a review). The impact of such neuroprotective agents on both psychological and neurocognitive functioning remains to be evaluated. The upsurge of interest in such neuroprotective procedures increases the need for further research into the neuropsychological impact of currently used variations of cisplatin-based therapies.

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