The Neuropsychiatry of Hematopoietic Stem Cell Transplantation

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ABSTRACT – *Background and Objectives:* Regimens incorporating hematopoietic stem cell transplantation (HSCT) have become widely utilized in disease treatments, particularly for cancer. These complex treatment programs also expose patients to central nervous system (CNS) toxicities from chemotherapy, irradiation, infection, metabolic effects and immunosuppression.

Methods: Relevant recent medical literature from Medline and bibliographies in pertinent publications are reviewed with a focus on those cases and studies pertaining to neuropsychiatric effects of HSCT.

Results: High rates of neuropsychiatric sequelae occur on a continuum from acute to chronic. Adverse outcomes include focal CNS deficits and severe global manifestations such as seizures, encephalopathy and delirium. More graduated effects on cognition, energy and mood are frequently seen, impacting patient function.

Conclusions: Additional research on neuropsychiatric outcomes and treatment interventions is needed in the HSCT setting. Risks for neuropsychiatric deficits should be part of an ongoing informed consent discussion among treating physicians, patients and families.

Introduction

Significant advances in therapy for multiple diseases of the blood cells and bone marrow have occurred over the last 3 decades. Many of the complex regimens developed to treat these entities involve the use of hematopoietic stem cell transplantation (HSCT). Approximately 50,000 trans-

plants were performed worldwide in 2002, with expected increases of 10-15% yearly (Goldman *et al.* 2002). Cells used in these regimens are harvested from self, related and unrelated donors and cord blood. Regimens utilizing these products involve typically marrow-diminishing applications of ionizing radiation and/or chemotherapy. Attempts are made to engraft the transplanted cells in an immunoreduced host –often with the hope for anti-tumor (graft-versus-tumor) effects from immunocompetent cells provided from the donor. Further efforts at immunomodulation are sometimes made to further reduce tumor burden or stimulate immune-system regeneration. In older or more medically frail patients, non-myeloablative regimens involving less toxic chemotherapy and radiation exposures have been more recently utilized (Geinstein *et al.* 2004).

Side effects, both acute and chronic, from these treatments are myriad. Acute effects include those related to immunosuppression, cytotoxicity and graft versus host disease. Chronically, graft versus host disease can develop, as well as sequalae affecting essentially every organ system. Different psychiatric syndromes may result from variations in the patient, type of illness treated, comorbid medical conditions, type of chemotherapy or radiotherapy and subsequent immunotherapy and resulting side effects (Appelbaum 2003).

Methods

We reviewed medical literature from MEDLINE (1980-2005) and bibliographies in pertinent publications for cases and studies regarding acute and long-term neuropsychiatric effects of HSCT in adults.

Many of these encompass neuropsychiatric syndromes outside the range of the American Psychiatric Association's Diagnostic and Statistic Manual (DSM) (Taylor *et al.* 2005). Our review included effects occurring on a continuum –from subtle emotional and cognitive problems to delirium and frank neurological deficits. Our search covered difficulties related to specific HSCT treatment agents and associated depression, anxiety, neuropsychological dysfunction and delirium.

Results

A range of conditioning therapies, often in combination, are used to destroy malignant cell and increase the potential for successful engraftment of donor cells. A number of neuropsychiatric effects have been noted with these regimens:

Radiotherapy

The effects of radiation are generally dependant upon dosage, duration, area targeted (whole body versus CNS) and any adjunctive chemotherapy. Much of the available literature cites outcomes for other cancer types. Armstrong *et al.* suggest the difficulty of estimating effects related to radiotherapy, chemotherapy or additive effects (Armstrong *et al.* 2004). Mechanisms for radiotherapy-related damage to CNS appear to be caused by factors beyond direct neuron apoptotic cell-death (Belka *et al.* 2001). Radiation may both elicit direct and indirect expression of cytokine mediators, including tumor necrosis factor (TNF)-alpha (Cammer 2000). These agents generate oligodendrocyte apoptosis and

reduction of progenitor stem cell populations (van der Maazen *et al.* 1991, van der Maazen *et al.* 1990). Belka *et al.* speculate that later neurotoxicity represents a failure of myelin recovery, (Belka *et al.* 2001) with additive contributions from radiotoxicity to vascular (Eissner *et al.* 1995) and subventricular cells (Tada *et al.* 1999).

Many regimens for HSCT employ total body irradiation (TBI) as preparative treatment. TBI may precipitate both acute and longer-term neuropsychiatric effects. Within 2 days to one week, short-term effects including drowsiness, heachache and emesis can appear. Subacutely, in 6 or more weeks, reversible fatigue and somnolence are complaints. Cases of transient somnolence and EEG background slowing have been noted subsequent to radiotherapy (Goldberg *et al.* 1992).

Longer-term deficits in reaction time, attention, concentration and difficulty with reasoning and problem-solving have been characterized as related to dosage of TBI administered (Andrykowski *et al.* 1990). Other prospective studies have suggested little change in cognitive function for cohorts followed longer-term (Wenz *et al.* 2000). Armstrong *et al.* point to the paucity of data covering outcomes for adult patients after several years. Older patients may be at higher risk for cognitive declines related to pre-existing vascular disease and medical comorbidity (Armstrong *et al.* 2004). White-matter lesions present at high rates (75-86%) in these patients (Wassenberg *et al.* 2001). Very high radiation dosing to focal CNS areas has been linked to necrotic effects resulting in focal neurological signs, seizures or increased intracranial pressure (Belka *et al.* 2001). Lastly, TBI may potentiate neurotoxicity from other immunosuppressive agents (Bartynski *et al.* 2004).

Chemotherapy

Different chemotherapeutic agents are often combined with other drugs and with radiotherapy to provide immunosuppression or ablation. Toxic effects of individual agents are therefore sometimes difficult to discern. Higher dosages often used with HSCT put patients at risk for neurotoxicity (Verstappen *et al.* 2003) or for adverse effects from other immunosuppressive agents (e.g. cyclosporine) (Bartynski *et al.* 2004). Most, if not all, have been implicated in at minimum subtle reversible cognitive disorder after transplantation (Syrjala *et al.* 2004a). Neuropsychiatric syndromes, primarily described in case studies, related to specific agents include:

Busulfan has been associated with seizures, particularly at higher dosages. Cases of abnormal EEG changes have been noted in patients undergoing HSCT (La Morgia *et al.* 2004).

Carmustine (BCNU) and the related alkylating agent *lomustine* (CCNU) generate toxicity generally at higher dosages as typical with HSCT. Cases of myeloencephalopathy and seizures evidencing over time after treatment have been noted in intra-arterial treatment for glioma, for which HSCT has been attempted (Mahaley *et al.* 1986).

Cisplatin, a platinum-containing antineoplastic, is commonly used for treatment of germ-cell tumors, from which much of the available literature has been derived. This agent has been linked to high incidence of peripheral neuropathy, averaging 57% in one survey (Tuxen *et al.* 1994). In an extensive literature, review, Troy *et al.* concluded that such involvement is primarily for large myelinated sensory fibers generating deficits for vibration, touch and occasional-

ly proprioception (Troy *et al.* 2000). Shock-like sensations descending along the legs and feet upon neck flexion (Lhermitte's sign) have been encountered with this agent (Inbar *et al.* 1992). Cisplatin-associated oto-toxicity at higher dosages occurs frequently, related to conduction delay in between the organ of Corti and the midbrain (Hansen *et al.* 1989). Patients may suffer ophthalmologic deficits, including blindness, (Cersosimo 1989) as well as autonomic neuropathy (Hansen 1990).

In addition to often dosage-related peripheral and cranial neuropathy syndromes (Siegal *et al.* 1990), cisplatin has been associated with rare encephalopathic conditions. Posterior leukoencephalopathy syndromes similar to those often related to immunosuppressive exposure have been noted. Symptoms have included seizures and central deficits such as cortical blindness. Reversible white-matter changes have been detected in occipital, parietal and frontal lobes (Ito *et al.* 1998, Lyass *et al.* 1998). Syndrome of inappropriate antidiuretic hormone (SIADH) with associated encephalopathy has also been noted in connection with this agent (Otsuka *et al.* 1996).

Troy *et al.* suggest the possibility for more subtle effects on higher-order functions such as visuospatial, reaction time, memory, verbal ability and executive processes. They draw analogy to other heavy-metal toxic syndromes and suggest risks to more sensitive areas of the hippocampus, amygdala, striatum and basal ganglia and frontal regions. Lastly, stroke-syndromes (in other cancer treatment regimens), appearing both ischemic and thrombotic in character, have been noted (Doll *et al.* 1986; Troy *et al.* 2000).

Cyclophosphamide and its analog, *ifosfamide,* both demonstrate neurotoxicity risks. Ifosfamide has been frequently connected to cases of encephalopathy with fairly rapid resolution. Prior history of cerebral events with ifosfamide, renal insufficiency or cotreatment with cisplatin, have been associated with risk for such mental status changes. Treatment with methylene blue and hydration may facilitate resolution (Di Maggio *et al.* 1994, Rieger *et al.* 2004). More rarely ifosfamide has generated syndromes involving seizures and focal events such as ataxia, cranial and peripheral neuropathy and extrapyramidal dysfunction (Klastersky 2003). Cyclophosphamide has been less commonly implicated in such effects in adults with cases of visual change and confusion at higher dosages observed (Kende *et al.* 1979).

Cytarabine-related cerebellar effects occur at higher dosages of this pyrimidine analogue and necessitate stopping this agent. Symptoms of somnolence and sometimes encephalopathy tend to precede an ataxia of variable severity. Damage to cerebellar Purkinje cells is implicated (Friedman *et al.* 2001). While the syndrome may resolve in some patients, age over 40, decreased liver and renal function or neurological dysfunction, may be risks for cerebellar injury. Signal-enhancement on magnetic resonance imaging (MRI) may precede clinical changes (Zawacki *et al.* 2000). Cytarabine has also been associated with cranial and peripheral neuropathy and brachial plexopathy, as well as a Guillian-Barré-like presentation (Osborne *et al.* 2004).

Etoposide has rarely been associated with peripheral neuropathy in HSCT (Imrie *et al.* 1994). Treatment for other cancers has been associated with effects such as confusion, seizures and focal effects including optic neuritis and cortical blindness, for which

HSCT patients may be at risk (Leff *et al.* 1988).

Fludarabine, a purine analog, has been occasionally associated at lower dosages with headache, somnolence, confusion and paresthesia, with delayed progressive encephalopathy common at higher dosages (Cheson *et al.* 1994, Warrell *et al.* 1986, Chun *et al.* 1986). Cases have been reported of progressive multifocal leukoencephalopathy (PML) (Gonzalez *et al.* 1999, Vidarsson *et al.* 2002). PML is characterized as a subacute demyelenating disease of the central nervous system (CNS) caused by reactivation of latent polyoma viruses (Padgett *et al.* 1983). Symptoms typically include progressive dementia, motor dysfunction, visual loss and often death (Wang 2004). Viral particles enter the CNS via oligodendrocytes and then enter glial cells via receptor-mediated clathrin-dependent endocytosis (Pho *et al.* 2000). MRI appearance in T_2-weighted images is generally seen as asymmetric nonenhancing bilateral bright lesions in the white and sometimes grey matter and brain stem, which may become confluent (Edelman *et al.* 1993).

Methotrexate's neurotoxic effects include aseptic meningitis and, particularly at higher dosages, encephalopathy involving progressive depression of consciousness and the development of seizures. These syndromes may present acutely or progress to more chronic, dementia-like conditions (Rubnitz *et al.* 1998, Walker *et al.* 1986). Most seriously, a leukoencephalopathy characterized by delayed deficits ranging from subtle learning difficulty to dementia with somnolence, gait disturbance, aphasia, hemiparesis and even death has been observed (Rubinstein *et al.* 1975). One series noted 26% of adult longer-term survivors of primary cerebral lymphoma with this devastating complication at 68 months

(Blay *et al.* 1998). Neuroimaging changes, including cerebral atrophy, diffuse white matter hyperintensities, ventricular enlargement and occasionally calcifications visible on MR imaging, may precede clinical effects (Lien *et al.* 1991).

Intrathecal methotrexate is associated acutely with high rates of arachnoiditis in 5-40% of patients. Symptoms include headache, nausea, vomiting, and meningeal signs with raised intracranial pressure. These may resolve over several days. Subacutely, intrathecal methotrexate can generate changes in mental status, progressive paraparesis and delirium (Brown *et al.* 1998). Chronic intrathecal methotrexate may generate a leukoencephalopathy similar to that caused by high-dose methotrexate (Moore *et al.* 2002). Methotrexate's neurotoxic effects may be the result of direct injury or of interference with folate metabolic pathways and the buildup of excitatory amino acid products (Vezmar *et al.* 2003).

Thiotepa has been implicated in neuropsychiatric effects such as progressive leukoencephalopathy, (Brown & Stoudemire 1998, Lai *et al.* 2004) particularly at higher dosages in combination with above agents. It has also been shown to elicit neurotoxic effects in animal studies (Rzeski *et al.* 2004).

Vincristine manifests dose-limiting peripheral neurotoxicity, related to interference with axonal microtubules and intracellular transport (Brown & Stoudemire 1998). More rarely, reports of intrathecal administration leading to fatal encephalopathy with myelopathy as well as delirium, seizures and cortical blindness have been noted (Tuxen & Hansen 1994). Encephalopathy has been seen in conjunction with SIADH induced by vincristine (Hammond *et al.* 2002, Hussain *et al.* 1993).

Immunomodulatory Therapy

In order to sustain a chemotherapeutic response or host anti-tumor immune effect or prevent graft-versus-host disease (GVHD), various agents have been employed. Agents with known neuropsychiatric effects and related syndromes include the following:

Corticosteroids act via the modulation and downregulation of lymphocytes and lymphocyte actions (Scudeletti *et al.* 1996). They have been well known since 1950 (Rome *et al.* 1950) as risks for a range of neuropsychiatric conditions. Corticosteroids have a role in both pretreatment chemotherapy for HSCT and suppression of GVHD. Neuropsychiatric syndromes related to steroid therapy represent a heterogeneous entity. Symptoms including mood changes or lability, frank mania, psychosis, depression, cognitive changes and delirium/confusion have been reported. Onset typically occurs within days to weeks and reverses with steroid taper (Lewis *et al.* 1983). EEG changes have been seen without characteristic pattern (Bleistein *et al.* 1989). Incidence rates, primarily drawn from treatment studies for other conditions, have been variable: 3-57% (Lewis *et al.* 1954, Lewis & Smith 1983, Sergent *et al.* 1975).

Most reviews have emphasized a predominance of mood-related changes; including both mania and depression. It is generally clinically inferred that mania predominates, although this has not been unanimous in the literature (Sirois 2003). Reports have also cited reversible dementia (Varney *et al.* 1984) and delirium (Stoudemire *et al.* 1996). The large Boston Collaborative Study established a threshold for neuropsychiatric effects as increasing markedly at doses above 80mg/day of prednisone (Acute adverse reactions to prednisone in relation to dosage 1972). Neuropsychiatric symptoms may also be precipitated by rapid steroid dosage changes and may not always correlate with absolute dosage. More subtle cognitive changes may occur, with studies showing short-term reversible decrement in auditory-verbal learning (Naber *et al.* 1996, Wolkowitz *et al.* 1990), and longer-term impairments in declarative memory function (Keenan *et al.* 1996, Newcomer *et al.* 1994). While there is currently little data on steroid-associated effects specifically in HSCT, corticosteroids have been shown to contribute to neurotoxicity syndromes with other immunomodulatory agents. Additionally, they may well contribute to longer-term functional difficulties experienced by cancer HSCT patients.

Cyclosporine (CSP), a calcineurin-mediated immunosuppressant, has well-documented association with neurotoxicity in other transplantation settings both acutely (Craven 1991) and long-term (Strouse *et al.* 1998). CSP has been found to lead to neurotoxicity at any point during HSCT, regardless of CSP blood levels; this effect is more likely in patients receiving more complex chemotherapy regimens (Bartynski *et al.* 2004, Edwards *et al.* 1996). In a series of 129 patients undergoing allogeneic HSCT, Trullemans *et al.* noted an incidence rate of 4.6% for neuropsychiatric effects –often with prodromal hypertension and headache occurring acutely/subacutely (3-37 days). Steroid and other preparative drug exposures were viewed as risk factors. They further noted in their study group seizures, symptoms of hemiparesis, and cortical blindness. Findings on MRI included cortical/subcortical white-matter hyperintensities –these suggest a local vascular etiology (Trullemans *et al.* 2001). Others have implicated microangiopathic phenomena in cyclosporine-related neurotoxicity (Bartynski *et al.* 1997, Pettitt *et al.* 1994). Risks for

cyclosporine-mediated toxicity include: HLA disparity, (Zimmer *et al.* 1998) hypocholesterolemia, hypomagnesemia, hypertension, acute renal failure, corticosteroid therapy, pre-treatment with etoposide, TBI, (Bartynski *et al.* 2004) acute GVHD and post-transplant microangiopathic hemolytic anemia (Pettitt & Clark 1994).

FK506 (Tacrolimus) also functions by means of calcineurin inhibition. Neuropsychiatric side effects have been well-documented in other populations, (Neuhaus *et al.* 1994) linked to impairment of the blood-brain barrier (Kaczmarek *et al.* 2003). Cases have also been noted in HSCT patients (Misawa *et al.* 2000). Posterior reversible encephalopathy syndrome (PRES) has been associated with both FK506 and CSP. This syndrome generally involves reversible imaging changes involving predominantly parietal and occipital lobe brain areas (Ay *et al.* 1998, Covarrubias *et al.* 2002, Hinchey *et al.* 1996, Mukherjee *et al.* 2001, Provenzale *et al.* 2001). Diffusion-weighted images on MRI have demonstrated vasogenic edema in areas of signal change and more rarely frank infarction (Covarrubias *et al.* 2002). Cases involving pretreatment with TBI may predispose for lesions into white matter versus those in cortical locations (Bartynski *et al.* 2001).

FK506 toxicity is likely associated with similar risks as in CSP toxicity (Zimmer *et al.* 1998, Cooper *et al.* 1989, Boogaerts *et al.* 1982, Bartynski *et al.* 2004). Lesions are heavily represented in critical cerebrovascular watershed areas. Investigators have therefore attributed aspects of PRES to hypertension (common during HSCT), (Mark 1990, Scherrer *et al.* 1990) vasospasm (Bartynski *et al.* 1997, Zimmer *et al.* 1998) and thrombotic microangiopathy (Holler *et al.* 1989). In a case review, Bartynski *et al.* suggest the role of a general endothelial injury process,

similar to eclampsia, generating vasospasm and resulting hypoxia. In their survey, for both CSP and FK506, onset occurred after days with most patients presenting with symptoms within the first month after HSCT, then additional peaks at 2-3 months and then later (5-13 months) (Bartynski *et al.* 2004).

Longer-term studies in aggregate have suggested that discontinuation of the implicated calcineurin inhibitor leads to resolution of neurological symptoms in the majority of cases (70% in one series after several months). Neurotoxicity after exposure to these agents often heralds the onset of GVHD and generally poor prognosis (Chohan *et al.* 2003). Although switching from CSP to FK506 has been attempted, it is not clear that this decreases the likelihood of neuropsychiatric problems (Neuhaus *et al.* 1994).

Granulocye macrophage stimulating factor (G-MSF) is utilized for treatment of neutropenia related to chemotherapy. G-MSF has also been associated with PRES, displaying MRI changes in the occipital and parietal regions (Leniger *et al.* 2000).

Interleukin-2 (IL-2) has been connected with neuropsychiatric effects in children (Classen *et al.* 2001) and in animal studies, possibly mediated by immune-cell infiltration (Hanisch *et al.* 1996). IL-2 effects have been noted on a continuum, from subtle alterations in energy and cognition to depression or mania (Strite *et al.* 1997, Walker *et al.* 1997). In treatment for other cancers, IL-2 has been associated with mental status changes, seizures and focal lesions (Karp *et al.* 1996). High case-rates have been reported for behavioral changes, including delirium, in 10-50% of patients receiving IL-2 infusions (Lerner *et al.* 1999).

Interferon-alpha, a naturally occurring inflammatory mediator, has been extensively used to treat other medical conditions, particularly hepatitis C. Recent protocols have utilized interferon-alpha in HSCT treatment (Aviles *et al.* 2005). The extensive database detailing neuropsychiatric risks from interferon-alpha is derived largely from its use for hepatitis C and to a lesser extent for malignancies such as malignant melanoma and renal cell carcinoma (Raison *et al.* 2005). These effects, likely related to interferon-alpha release during chemotherapies, may be of concern for use in HSCT.

During treatment for other malignancies, interferon-alpha has been implicated in acute confusional states (delirium), disorientation, lethargy, somnolence, psychomotor retardation, aphasia and agraphia, and psychosis (Adams *et al.* 1988, Farkkila *et al.* 1984, Iivanainen *et al.* 1985, Mattson *et al.* 1983, Meyers *et al.* 1991, Niiranen *et al.* 1988, Poutiainen *et al.* 1994, Rohatiner *et al.* 1983, Smedley *et al.* 1983). These changes have occasionally been noted as persisting beyond discontinuation (Meyers *et al.* 1991). It has been theorized that rapid onset toxic effects may correlate with interferon-alpha's stimulation of opioid receptors or alterations in dopamine turnover (Schaefer *et al.* 2003).

Mood symptoms have been most notoriously connected with the employment of interferon-alpha. Depressogenic effects of interferon-alpha have been attributed to alterations in central serotonin neurotransmission. These changes may be occurring directly, related to changes in 5-HT_2 receptor function or via alterations in the metabolism of the serotonin precursor tryptophan (Menkes & MacDonald 2000, Taylor & Feng 1991, Yang *et al.* 2004).

Alternatively, the group led by Capuron has delineated a split in onset between more purely neurovegetative and somatic symptoms versus those of mood, anxiety and cognition. In a study observing treatment for malignant melanoma, features of altered sleep, pain, anorexia and fatigue occurred after 2 weeks with features of depression developing later (Capuron *et al.* 2002). Capuron suggests in further work the possible role of induction of depression via interferon-alpha's induction of corticotropin-releasing factor (CRF). CRF is implicated in some forms of endogenous depression, and Capuron links this association (Owens *et al.* 1993) to the responsiveness of interferon-alpha-induced depression to antidepressant therapies (Musselman *et al.* 2001). By contrast, more purely neurovegetative interferon-alpha-induced symptoms appear more resistant to antidepressants (Capuron 2004). These somatic symptoms are suggested to occur separately as part of the general proinflammatory response common in medical illness: a so-called "sickness-syndrome" (Dantzer 2005). Much less commonly, symptoms of mania have occurred as part of interferon-alpha therapy or withdrawal (Carpiniello *et al.* 1998, Monji *et al.* 1998).

Rituximab directs an antibody against the CD20+ receptor facilitating immunusuppression. Rituximab-associated cases of infection with JC papovavirus or cytomegalovirus (CMV) have been recorded in autologous and allogeneic (Steurer *et al.* 2003) HSCT patients. Matteuchi *et al.* report a diagnosis of PML in a patient with non-Hodgkins's lymphoma (NHL) heavily pretreated with sequential rounds of chemotherapy. This case involved the onset of mental status changes and ataxia several months post-transplant (Matteucci *et al.* 2002).

Goldberg and co-investigators also cite two cases of PML after HSCT and Rituximab with a similar clinical course, and they review the better-known occurrence of PML in other states of immunosuppression (i.e. HIV) and delayed T-cell reconstitution (Goldberg *et al.* 2002). Both cidofir and IL-2 have been tried in treatment of PML (Osorio *et al.* 2002, Shitrit *et al.* 2005). Perhaps by increasing CD4+ count, IL-2 has shown some benefit (Buckanovich *et al.* 2002).

Global Clinical Syndromes

Neuropsychological and Functional Changes:

Subjective complaints of cognitive difficulty –sometimes referred to as "chemobrain"– are common acutely and longer-term for cancer patients. Difficulties quantifying these deficits arise due to challenges assessing baseline cognition, effects related to the cancer itself and influences of comorbid medical conditions. Not uncommonly, HSCT populations have demonstrated cognitive deficits, prior to transplantation, compared to medically-ill controls, likely related to severe underlying medical illness and prior treatment (Andrykowski *et al.* 1992, Harder *et al.* 2005). Results may vary based upon time of sampling (acute versus chronic) or the instrument used to assess cognitive function.

An extensive recent review by Anderson-Hanley *et al.* highlighted some of these methodological challenges. They attempted to look at neuropsychological difficulties studied for cancer patients in aggregate. They note the challenge of making comparison between patients and controls versus pretreatment and post-treatment. Over the domains of executive, verbal, motor and memory functioning, they note statistically significant impairments compared with control subjects and normative data. They suggest these effect sizes as medium to large for executive and verbal memory and small to large for motor function. Anderson-Hanley *et al.* acknowledge that these results exclude patients receiving direct brain irradiation or more intensive and higher-dosage regimens (Anderson-Hanley *et al.* 2003).

It would be expected that more intensive HSCT conditioning regimens would be more likely to create cognitive and functional deficits. This appears to have been confirmed by other studies of neuropsychiatric risks from radiation or intrathecal chemotherapy in the generation of subsequent deficits. These cognitive effects particularly target higher-order processes (e.g. executive function) and are likely additive (Andrykowski *et al.* 1989). It is concerning that measures of cognitive ability (Trail-making Test Part B, Controlled Oral Word Association Test) demonstrate declines in executive processing over the acute course of HSCT. In a study by Ahles, these declines were in contrast to general improvement in levels of anxiety and depression (Ahles *et al.* 1996). Carefully assessing cognitive performance over the course of transplant and at intervals of 80 days and one year post-transplant, Syrjala *et al.* noted deficits globally in cognitive function. These spanned the domains of attention, information processing speed, learning, visual-motor integration, verbal fluency and verbal memory. Patients experienced nearly uniform returns close to pre-treatment performance baselines after one year (Syrjala *et al.* 2004a).

As a proxy for global physical, cognitive and emotional function, the majority of studies have reported high rates of return to work, ranging from 60% -84%, several years after transplantation (Syrjala *et al.* 1993, Bush *et al.* 2000, Hensel *et al.* 2002, Syrjala *et al.* 2004b). There is however,

some implication of a "ceiling effect" in functional attainment and quality of life (Andrykowski *et al.* 1989). Despite high levels of return to work or school, significant numbers of patients report high levels of cognitive fatigue even three years after HSCT (Hjermstad *et al.* 2004).

Depression and Anxiety:

Rates of reported depression are likely influenced to some degree by the screening instrument employed and specificity of diagnosis (e.g. using rating scale cutoff points versus clinical diagnosis). Pre-transplant factors related to illness severity, social support, coping style and pre-existing depression may also weigh heavily on depression incidence (Grassi *et al.* 1996, Massie *et al.* 1998). Patients may present pre-transplant with elevated rates of depressive symptoms. During HSCT distress may further increase: 18% depressive symptom rates noted in one survey (Vose *et al.* 1992). These symptoms include changes in acute distress that may not meet formal criteria disorder for a DSM-IV diagnosis of a major depressive or anxiety disorder.

In a study focused specifically on patients hospitalized for HSCT, Prieto *et al.* reported significantly elevated rates of initial anxiety, which resolved as patients' anticipated fears for treatment were addressed. This was in contrast to depressive symptoms which rose at 7 days into HSCT and closely paralleled physical distress. Mood improved, as did physical health status, as treatment progressed (Prieto *et al.* 2005b). Post-traumatic stress symptoms assessed in a cohort by Wettergren *et al.* were elevated in a cohort followed through HSCT, with improvement over time (Wettergren *et al.* 1999). Similar findings were observed for lymphoma patients with elevated rates of depression,

correlated with fatigue, occurring at day 7 (El-Banna *et al.* 2004).

A group led by Hjermstad outlined a trajectory for mood complaints 2-4 weeks pre-transplantation, with consistent return to baseline levels after 4 months. They concluded that somatic complaints were a driver for depression (Hjermstad *et al.* 1999). Later work has charted high rates of cumulative psychiatric symptoms, including combined adjustment, mood and anxiety disorders (42.3% using DSM-IV criteria), with associated increased hospital length of stay for HSCT (Prieto *et al.* 2002). Although rates of anxiety and depression decline over time in most surveys, they are likely related to physical symptoms. Depression and distress adversely impact functioning after transplantation (Lee *et al.* 2005, Meyers *et al.* 1994).

Fatigue related to cancer is a subjective and multidimensional phenomenon impacting physical and cognitive functioning and likely overlaps with depression. Rates of fatigue during cancer treatment generally range from 25% to 99% and are higher than controls during HSCT (Blesch *et al.* 1991, Hann *et al.* 1999, Monga *et al.* 1999). Patients relate impacts on daily and employment function related to high levels of unaddressed fatigue (Curt *et al.* 2000, Vogelzang *et al.* 1997). Etiology may relate to effects of elevated levels of cytokines on the CNS hypothalamic-pituitary axis or possibly a T-cell mediated inflammatory process (Bower *et al.* 2005, Bower *et al.* 2002, Bower *et al.* 2003).

Studies have attempted to follow individuals longer term after HSCT for symptoms of psychological distress. Researchers have attributed greater levels of depressive symptoms in the period from hospital discharge to 100 days after HSCT to correlate with

adjustment into more normal life. Depression and other markers for distress may be subject to influences from other life stressors and changes in support (McQuellon 1998). In a cohort of patients treated with HSCT for CML, Chang *et al.* saw overall levels of depressive symptoms and alcohol usage decline over time. Declines in Beck Depression Inventory scores were statistically significant. They note higher quality of life related to younger age and more prestigious employment status (Chang *et al.* 2005).

Symptoms of depression during transplantation were not found by Chang's group to affect 1-year survival, although they were associated with higher death-rates in the subsequent 1-2.5 year period (Chang *et al.* 2004; Chang *et al.* 2005). Others have found elevated risks for mortality associated with depression in the 6-12 month period after HSCT, after controlling for transplant type and medical risks, (Loberiza *et al.* 2002) and recently have shown greater risk for dying in those patients with major depression at 1 and 3 year follow-up (Prieto *et al.* 2005a).

Rates of anxiety may remain elevated in HSCT patients after one year compared to the general population (Hjermstad *et al.* 1999). Syrjala *et al.* suggest delay in emotional recovery compared to physical improvement. They note 22% of patients meeting criteria for clinical depression within a five-year period after HSCT. Similar to the general population and other studies in HSCT, they related higher risk for women after treatment (Heinonen *et al.* 2001, Syrjala *et al.* 2004b). A review by Neitzert *et al.* across multiple studies, populations and time-points was consistent for elevated levels of depression and psychosocial distress. HSCT patients appeared on a range of time-scales to be doing more poorly than either normal controls or patients undergoing other cancer treatments. They note the difficulty of drawing conclusions from varied sources and methods (Neitzert *et al.* 1998). Studies at 3 years out have not uniformly noted high levels of post-transplant depressive or anxiety symptoms, however (Hjermstad *et al.* 2004). Finally, difficulties with emotional adjustment after HSCT also correlate with significant post-transplantation fatigue (Knobel *et al.* 2000).

While a recent review (Spiegel *et al.* 2003) suggests the relationship of depression to cancer incidence remains ambiguous, it is clear that mood symptoms adversely affect patient outcomes. Cancer progression may be related to poor adherence and self care (Pirl *et al.* 1999). Direct effects mediated through hormonal and immune axes related to depression may theoretically promote cancer progression. Studies have suggested levels of chronic HPA axis activation often characteristic of depression (Yehuda *et al.* 1996) reducing T-cell mediated immune responses (Moynihan 2003) and affecting natural killer cell immune surveillance (Davis *et al.* 2001). This is more consistently seen in states of chronic versus acute stress (Levy *et al.* 1987). Animal models have shown rapid cancer growth in animals with surgically blunted cortisol rhythm (Filipski *et al.* 2002). Elevated levels of glucocorticoid hormones seen in depression may suppress existing immune response (Callewaert *et al.* 1991) or accelerate tumor metabolism. (Rowse *et al.* 1992).

Data in depressed humans show a general trend towards suppression of immune and particularly natural killer cell function. Depression-mediated suppression of MHC-1 receptors on tumor cell surfaces may permit these to escape destruction by the immune system (Reiche *et al.* 2004). These

findings may help explain alterations in outcome related to depression or distress in HSCT (Levav *et al.* 2000). Lastly, alterations of cellular DNA repair and dysregulation of cell apoptosis associated with distress may facilitate cancer progression (Kiecolt-Glaser *et al.* 1985, Tomei *et al.* 1990). Ultimately, a "bidirectional model" may prevail: aspects of cancer stress and treatment (such as interferon-alpha) and immune changes influencing depression incidence, and depression likewise altering immune function (Reiche *et al.* 2004).

Delirium:

The syndrome of delirium presents as one of the most significant neuropsychiatric concerns in HSCT. Delirium is defined as a constellation of acute changes involving level of consciousness, attention, cognition and perception often with symptom fluctuation, linked to concomitant medical conditions, medications or other substances (American Psychiatric Association, 2000). Associated EEG changes typically show loss of alpha rhythm and its replacement by theta and delta waves over posterior areas, with possible dysfunction of attentional networks associated with the anterior cingulate cortex (Jacobson *et al.* 2000, Reischies *et al.* 2005).

Given risks from chemotherapy, immunusuppression, infections, medications and associated metabolic and medical comorbidities, it is not surprising that high rates of delirium have been noted in HSCT – up to 50% in one study (Fann *et al.* 2002). A recent study cited incidence as 18% during hospitalization in non-terminally ill patients, which increased length of stay (Ljubisavljevic *et al.* 2003). Etiology is typically multifactorial (Fann *et al.* 2003). Agents commonly used in cancer treatment with strong linkage to delirium include opi-oid analgesics, sedatives, corticosteroids and anticholinergic medications (Han *et al.* 2001).

In hospitalized cohorts with malignancies, delirium has been associated with increased mortality ratios of 6.2 during hospitalization and 14.1 1-5 years afterwards (van Hemert *et al.* 1994). Delirium in advanced stage cancers and terminal illness has been strongly associated with shortened time of survival (Caraceni *et al.* 2000, Metitieri *et al.* 2000, Morita *et al.* 1999). On a consultation-liaison service, Olofsson found higher incidence, shorter duration and better prognosis in those patients presenting with the hyperalert delirium variant. It was also found that treatment of delirium was associated with better outcome (Olofsson *et al.* 1996).

Studies more closely examining delirium in HSCT populations have suggested high rates of distress (Breitbart *et al.* 2002) and incidence typically within 4 weeks post-transplantation (Fann *et al*, 2002, Prieto *et al.* 2005b). Delirium risks in severely immuno-compromised HSCT patients include encephalitis related to reactivation of latent human herpes virus 6 (HHV-6), varicella-zoster and CMV (Hackanson *et al.* 2005, Hentrich *et al.* 2005, Julin *et al.* 2002). HHV-6 encephalitis may also present with behavioral changes and nonspecific MRI findings (Muta *et al.* 2005, Tsujimura *et al.* 1998, Zerr *et al.* 2005). Fann *et al.* recorded delirium in HSCT marked by disturbance of sleep-wake cycle, psychomotor abnormality and degraded cognitive function. Incidence rates for delirium episodes were 50% with average duration of 10 days. Symptoms of frank psychosis were rare, and delirious patients evidenced higher rates of fatigue, pain and affective distress than non-delirious patients. The predominant psychomotor presentation was of a more hypoactive delirium in 86% of

such patients. Fann's group found three primary delirium symptom domains in psychosis/behavior, cognition and mood/level of consciousness. They noted prodromal symptoms involving attention, disturbed perceptions, and changes in cognition peaking at approximately 2 weeks post-transplantation preceding frank delirium (Fann *et al.* 2005).

Table I
Summary of Neuropsychiatric Effects from Specific Agents Utilized in HCST.

Agent	Acute/Sub-acute Effects	Long-term Effects
Radiotherapy	Emesis, drowsiness, headache, fatigue, somnolence.	Cognitive deficits, focal signs, seizures, increased ICP (high dosage).
Chemotherapy		
Busulfan	Seizures.	
Carmustine (BCNU)/ *lomustine* (CCNU)	Seizures, myeloencephalopathy	Cognitive deficits
Cisplatin	Peripheral/cranial/autonomic neuropathy, ototoxicity, leukoencephalopathy, seizures, SIADH, stroke-like episodes.	
Cyclophosphamide	Visual changes, confusion.	
Cytarabine	Somnolence, ataxia, peripheral/cranial neuropathy, Guillian- Barré Syndrome.	
Etoposide	Peripheral neuropathy, confusion, seizures, optic neuritis, cortical blindness.	
Fludarabine	Headache, somnolence, confusion, paresthesia, PML.	
Ifosfamide	Encephalopathy, seizures, focal deficits	
Methotrexate	Arachnoiditis, aseptic meningitis, leukoenphalopathy, seizures, paraparesis, delirium (especially intrathecal).	Dementia-like changes. Leukoencephalopathy (especially intrathecal).
Thiotepa	Leukoencephalopathy.	
Vincristine	Peripheral neuropathy, encephalopathy, SIADH.	
Immunomodulatory Therapy		
Corticosteroids	Mood lability, mania, depression, psychosis, delirium, cognitive deficits.	
Cyclosporine	Headache, seizures, focal deficits, cortical blindness, PRES.	
FK506	PRES.	
G-MSF	PRES.	
Interleukin-2	Behavioral changes, delirium, fatigue, depression, mania, cognitive deficits, seizures, focal changes.	
Interferon-alpha	Delirium, somnolence, depression, aphasia, agraphia, psychosis.	Cognitive deficits.
Rituximab	PML.	

ICP = Intracranial pressure, PML = progressive multifocal leukoencephalopathy, PRES = posterior reversible encephalopathy syndrome, SIADH = Syndrome of inappropriate anti-diuretic hormone.

Discussion

Patients undergoing HSCT are subject to a range of neurotoxicities of varying severity and duration. Future studies should aim towards standardizing symptom rating instruments and controlling for pertinent treatment-related variables (e.g. allogeneic/autologous transplant status, prior chemotherapy exposure, age and comorbid medical illnesses) (Neitzert *et al.* 1998). More recently, research has moved in the direction of close longitudinal screening and quantification of risk factors for sensitivity to specific agents or clinical syndromes (Neitzert *et al.* 1998, Fann *et al.* 2002, Syrjala *et al.* 2004b). For example, it would be helpful to know which patients are susceptible to CSP-mediated leukoencephalopathy and consider potential CNS-sparing regimens (Forgacs *et al.* 2005, Maramattom *et al.* 2004). High rates of emotional distress, acutely and longer-term, suggest the role of more routine and systematized pre-transplantation evaluation and further outcomes research examining currently used and new treatment approaches (Rush *et al.* 2004).

Studies of neuroprotection or cognitive rehabilitation are in a period of relative infancy. Given the high prevalence of global neuropsychiatric deficits, trials are needed to clarify risk factors (Ahles *et al.* 2003) and to elucidate the role of agents with probable ameliorative or preventative benefit (O'Shaughnessy *et al.* 2005, Thompson *et al.* 2001). Alternatively, regimens with relatively high margins for safety could be assessed for efficacy in relief of cognitive disorder after initial onset (Cimprich *et al.* 2003). Finally, additional research into the neuropsychiatric sequelae of long-term survivors of HSCT is needed, particularly within the growing numbers of patients receiving nonmyeloablative conditioning regimens.

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