Annals of Oncology 19: 623–629, 2008
doi:10.1093/annonc/mdm500
Published online 31 October 2007

Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop

J. Vardy[1], J. S. Wefel[2], T. Ahles[3], I. F. Tannock[4] & S. B. Schagen[5]*

[1]*Sydney Cancer Centre, Concord Repatriation General Hospital, Cancer Institute, New South Wales, Australia;* [2]*Department of Neuro-Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX;* [3]*Department of Psychiatry and Behavioural Sciences, Memorial Sloan-Kettering Cancer Center, New York, NY, USA;* [4]*Department of Medical Oncology and Hematology, Princess Margaret Hospital and University of Toronto, Toronto, Ontario, Canada;* [5]*Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

Received 3 September 2007; accepted 27 September 2007

A subset of survivors has cognitive impairment after cancer treatment. This is generally subtle, but may be sustained. In October 2006, the second international cognitive workshop was held in Venice. The workshop included neuropsychologists, clinical and experimental psychologists, medical oncologists, imaging experts, and patient advocates. The main developments since the first Cognitive Workshop in 2003 have been the following. (i) studies evaluating cognitive function in patients receiving chemotherapy for cancers other than breast cancer, and in patients receiving hormonal therapy for cancer. (ii) The publication of longitudinal prospective studies which have shown that some patients already exhibit cognitive impairment on neuropsychological testing before receiving chemotherapy, and some patients have deterioration in cognitive functioning from pre- to postchemotherapy. (iii) Studies of the underlying mechanisms of cognitive impairment both in patients and in animal models. (iv) Use of structural and functional imaging techniques to study changes in brain morphology and activation patterns associated with chemotherapy. (v) At present cognitive research in cancer is limited by methodological challenges and the lack of standardization in neuropsychological studies. The current workshop addressed many of these issues and established an international task force to provide guidelines for future research and information on how best to manage these symptoms.
Key words: chemotherapy, cognition, neurotoxicity, side-effects, systemic therapy

introduction

The first international workshop on cognitive function in adult cancer survivors (Banff, Canada, 2003) focused on chemotherapy-induced cognitive changes secondary to adjuvant chemotherapy for breast cancer [1]. In October 2006, a second workshop was held in Venice, Italy with 50 participants (see appendix) and had an expanded focus on various cancers (breast, testicular, and prostate) and treatments (chemotherapy and hormonal therapy). Emerging evidence indicates that cancer *per se* and/or cancer treatments in addition to chemotherapy may contribute to cognitive impairment, so a more encompassing term is required to describe this condition. Persistent cognitive changes associated with chemotherapy and/or hormonal therapy are often subtle, but can impact on survivors' ability to function. Treatments which can have a more profound effect on cognitive functioning (e.g. cranial surgery and/or radiation therapy, interferon) were not discussed.

The main aims of the Venice workshop were to present ongoing research, with a focus on putative mechanisms; to forge new collaborations; to discuss the methodological problems associated with cognitive research; and to establish an international task force to provide guidelines for future research, as well as information for clinicians and patients on the management of these symptoms. This article provides a summary of the 2006 cognitive workshop, and a description of the mission of the newly formed International Cognition and Cancer Task Force (ICCTF). It will focus on chemotherapy-induced cognitive changes although many of the methodological and mechanistic issues are relevant to the study of other cancer treatments.

brief overview of the existing literature

Several reviews and meta-analyses [2–5] have concluded that there is evidence for cognitive changes associated with cancer and cancer treatments, but have identified methodological

Correspondence to: Dr S. B. Schagen, Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel: +31-20-5122480; Fax: +31-20-5122322; E-mail: s.schagen@nki.nl

problems with many of the published studies [6]. Earlier studies reported cognitive impairment in 15%–50% of adult solid tumor survivors who had received chemotherapy [1,7–12]. These studies indicate that cognitive deficits are diffuse, and involve the domains of attention and concentration, verbal and visual memory, and processing speed [9–11, 13, 14]. Most of these studies were limited by sample size and were cross-sectional in design, with no evaluation of cognitive function before treatment and no longitudinal data.

summary of developments in cognitive research in cancer since the first workshop

At the first Workshop in 2003, participants highlighted the need for prospective longitudinal cognitive studies to better quantify the incidence of cognitive decline after chemotherapy. Subsequently, a small number of prospective, longitudinal studies have been published. Some have reported a decline in cognitive function after chemotherapy [15–18] while others show no significant change [19]. This discrepancy may reflect the different chemotherapy regimens administered and/or methodological problems relating to the design and analysis of the studies (e.g. variations in normative data and reference groups, statistical cut-offs used to define cognitive impairment, use or not of corrections for practice effect and of alternate forms of neuropsychological tests to minimize practice effect and control for test–retest variability in comparable with people not undergoing chemotherapy). The earlier studies consistently reported that the cognitive sequelae was diffuse, and relatively nonspecific in nature. However, evidence from new studies indicates a frontal, subcortical toxicity profile, with cognitive dysfunction within domains of information and processing speed, attention, memory retrieval, and executive function.

Consistent with reports in the literature [20], most investigators conducting longitudinal studies described lower than expected cognitive performance before receiving adjuvant treatment. Most reported a general improvement in cognitive performance with repeated testing, but found that a subset of survivors either declined or failed to achieve the expected practice effect. This reinforces the need for an appropriate comparison group (see below) and analytic techniques to account for practice effect.

Assessment of patients soon after diagnosis of cancer is difficult, and the stress of receiving the diagnosis of a potentially lethal illness, as well as the effects of a recent anesthetic and surgery, may confound the interpretation of baseline tests of cognitive function. However, the cognitive performance of patients assessed after surgery but before subsequent treatment, did not appear to be associated with factors such as depression, distress, anxiety, or fatigue; deficits in cognitive performance have also been documented following diagnosis but before surgery [16, 20, 21].

These results indicate that there may be some aspects of the cancer (e.g. elevated proinflammatory cytokines) that impacts cognitive performance, and/or that there may be common risk factors (e.g. inefficient DNA repair mechanisms) associated with the development of cancer and of neurocognitive problems [22].

Since the last workshop, there have been studies of potential adverse effects on cognitive function of cytotoxic regimens other than those applied in the treatment for breast cancer (e.g. colorectal cancer, testicular cancer) as well as studies of the effects of hormonal treatments in different cancer populations. Cognitive impairment following cancer treatment has been accepted as a survivorship issue and translational studies have been initiated to study underlying mechanisms in patients (using blood tests and imaging) and in animal models. The combination of mechanistic with behavioral studies has enabled researchers to design more hypothesis-driven research.

methodological challenges in cognitive assessment

Despite growing insight into the association between chemotherapy and cognitive functioning, the characterization of cognitive impairment in terms of its nature, course over time, underlying mechanisms and impact on subject's lives is still limited. These deficiencies in knowledge may be a corollary of the relative infancy of the research field, but progress is hampered by variability in extant literature on the cytotoxic regimens involved, study design, and neuropsychological measures and methods employed [6]. In particular, variation between studies in criteria used for defining cognitive impairment makes it impossible to define the prevalence of cognitive impairment.

The methodological session of the second Workshop was designed to promote optimization and standardization of study design and to formulate priority topics for future working groups.

The guest speaker, Dr R. K. Heaton (San Diego) has been instrumental in developing consensus initiatives on cognitive measurement and treatment in other patient populations (especially Human Immunodeficiency Virus), and has published normative data for numerous neuropsychological tests. Dr Heaton discussed the selection of appropriate neurocognitive tests in terms of the sensitivity of the batteries to detect mild deficits; the need to assess a variety of cognitive domains; the source of normative standards to discriminate between normal and abnormal performance; and the selection of test score- and test battery-cut-offs in determining impairment. He paid particular attention to selection of cognitive tests for longitudinal studies, such as their performance on repeated application, including test–retest reliability and practice effect. He addressed the difficulty of finding appropriate norms for detecting cognitive change on tests, and the sensitivity of different prediction models for detecting real change.

Based on Dr Heaton's experience developing consensus guidelines in HIV-consortia, he made the following recommendations: (i) neuropsychological test batteries should evaluate multiple domains of cognitive ability; (ii) test results should be corrected for age, education, gender and where

appropriate ethnicity; (iii) summary or 'global'deficit scores [23] often are preferable to analyzing individual test scores or averaging scores on the neuropsychological battery, because impairments may occur on different patterns of tests for different people, (summary deficit scores focus on problems wherever they appear, circumventing situations where good performance on some tests may obscure deficits in other areas); (iv) for cross-sectional data, it may be helpful to use global deficit scores to determine and compare percentages of people who are 'impaired' within the study groups, as both disease effects and negative treatment effects on cognition may be present in only a subset of patients [24]; (v) impairment on an individual test or summary score should require a score of one standard deviation below the mean of a control group, as this cut-off provides the optimum balance between sensitivity and specificity [25]; (vi) in longitudinal studies, tests should be selected based on considerations of test reliability, practice effects (including availability of alternate forms), and sensitivity to measuring change; (vii) for the classification of change, one should use a reliable change index (RCI) or regression-based model that accounts for practice effect and normal test–retest variability [26], employing longitudinal data from an appropriate control group, with a confidence interval (CI) of 90%; (viii) an overall classification of change could be based upon test–retest differences in the chosen summary score. Alternatively, this can be determined by subtracting the number of individual scores on the test battery below the 90% CI from those above the 90% CI, the comparison group's distribution of these difference scores is then used to develop cut-offs to define whether overall improvement or deterioration has occurred; (ix) as healthy controls tend to have less test variability than clinical controls, studies should use concurrent controls that closely resemble patients, rather than published normative data; and (x) as baseline scores are strong predictors of retest scores, and participants with low baseline test performances tend to have greater test–retest variability, it may be advisable to use different norms for change in cognitive function for patients with low baseline functioning.

The ensuing discussion focused on indicated principles for researchers to consider when developing and analyzing their studies. The discussion centered on four topics.

cross-sectional versus prospective study design

The selection of study design should be dependent on the research question. Certain constraints, such as investigating long-term/late effects of cancer treatment or treatment effects for rarer cancers, may make well-controlled, cross-sectional designs the most feasible approach. However, wherever possible, longitudinal studies offer important additional information on pretreatment cognitive status and change over time. As cancer treatment is an anticipated therapy it provides an opportunity to prospectively monitor cognitive function to determine whether the treatment produces neurocognitive sequelae.

the choice of reference groups

The best controls are those that closely resemble the target group i.e. disease-specific controls or controls experiencing a major life event (for example, in studying the effects of chemotherapy an optimal control group might consist of patients with a similar type of cancer who received only local treatment). Healthy controls may also be included, but preferably in addition to a disease-specific reference group. Very rigorous exclusion criteria should probably not be used in selecting healthy controls (such as history of mild psychiatric or other illness, concussion) as these conditions are often present in target groups.

selection of cognitive domains and neuropsychological tests

Whether current knowledge on the cognitive effects of chemotherapy provides sufficient evidence to narrow the assessment to particular domains is arguable. Although the imaging studies are reporting fairly diffuse changes in brain structure and activation (see below), most participants agreed that the deficits found on neuropsychological testing indicate a frontal–subcortical profile. Therefore a working group should provide recommendations of core domains to be evaluated based on this working hypothesis, and on specified criteria of reliability and validity. An additional suggestion was for future publications to provide information on the properties of selected tests, as well as specify a minimal set of outcome variables reported by all researchers who employ these tests, to allow for meta-analysis regarding affected domains.

criteria for cognitive impairment and change

There are numerous methods to determine what constitutes abnormal performance. Individual test or domain scores can be used, and different cut-off points selected per test and/or test battery. With regard to prospective studies, several prediction models for change are available, but use of either an RCI model that accounts for practice effect (preferably based on people with similar baseline functioning as the interest group) with a 90% CI, or a regression model were recommended. Participants agreed on the need for guidelines on methodologies and criteria for determining cognitive dysfunction and change in cognitive function across time, with attention to both objective measures of cognitive function as well as subjective reports of cognitive function.

mechanisms of chemotherapy-associated cognitive changes

The etiology of cognitive impairment after chemotherapy remains unknown although a number of mechanisms have been postulated [22]. (See Figure 1). Candidate mechanisms include: direct neurotoxic effects (e.g. injury to neurons or surrounding cells, altered neurotransmitter levels) [22,27–30]; oxidative stress and DNA damage [22, 31, 32]; induced hormonal changes [33]; immune dysregulation and/or release of cytokines [22, 31, 34]; and blood clotting in small central nervous system (CNS) vessels. Some patients may have a genetic predisposition to developing cognitive impairment (see discussion below).

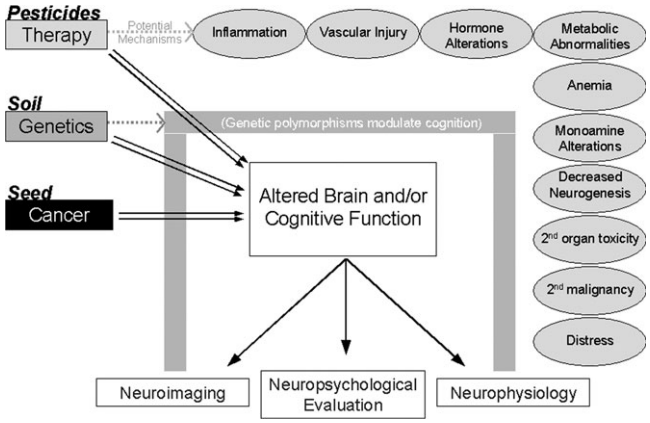

Figure 1. Postulated mechanisms of chemotherapy-associated cognitive changes.

imaging/electrophysiological studies

Several participants at the workshop (Silverman, Tannock, Vardy, and Ahles) described on-going and published studies of changes in brain morphology and activation patterns .associated with chemotherapy utilizing both structural and functional imaging techniques. Studies using magnetic resonance imaging (MRI) have reported reduced volume of brain structures important for executive functioning (e.g. frontal cortex) and changes in the integrity of white matter tracts in patients treated with chemotherapy [29, 35, 36]. However, one study that examined hippocampal volume found no volumetric differences when comparing breast cancer patients treated with chemotherapy to those not treated with chemotherapy [37]. Early results from a functional MRI study revealed a pattern of reduced activation in frontal cortex during a working memory task in patients treated with chemotherapy compared with patients not treated with chemotherapy and healthy controls [38]. Dr Silverman presented a study using Oxygen-15 positron emission tomography that demonstrated that breast cancer patients treated with chemotherapy, when compared with breast cancer patients who received no chemotherapy and healthy controls, showed increased metabolic activity in the prefrontal cortex during a cued recall memory task [39]. Additional evidence for compensatory activation of brain structures not typically utilized for a given cognitive task has also been reported [39–41], raising the possibility that performance on neuropsychological testing may remain in the normal range through altered activation brain patterns. Finally, Dr Kreukels presented electrophysiologic studies examining the P-300 event-related brain potential and reported decreases in amplitude (intensity of neural activation) and latency (timing and duration of activation) of P-300 associated with chemotherapy, which is consistent with changes in information processing capacity [42, 43]. Taken together, these data indicate that chemotherapy is associated with changes in brain structure and function.

animal models

Research examining the impact of chemotherapy on learning and memory in animal models was presented (Winocur, Buwalda). Recent studies have demonstrated that commonly used chemotherapy agents, administered peripherally, can cause disruption of learning and memory across a variety of tasks (Morris Water Maze, avoidance conditioning, cue-specific and contextual fear conditioning tasks) in both mouse [44, 45] and rat models [46, 47]. In contrast, one study did not find any detrimental effects of treatment with 5-fluorouracil on rat behavior [48]. Studies utilizing histological analyses of the brain of animals that received chemotherapy have demonstrated cell death and slowing of cell division in structures critical for memory and learning, including the subventricular zone, the dentate gyrus of the hippocampus, and the corpus callosum [30, 49].

cytokines

One potential mechanism leading to cognitive dysfunction (and fatigue) is the stimulation of cytokines by cancer and chemotherapy. Treatments that stimulate cytokine production (e.g. interferon) have been associated with a variety of symptoms, including cognitive deficits [50, 51]. Further, patients with hematological malignancies were found to have elevated levels of interleukin-1 (IL-1), IL-1 receptor agonist, IL-6, IL-8, and tumor necrosis factor-alpha compared with normative values before treatment and higher levels of IL-6 were associated with poorer performance on measures of executive function before treatment [52]. Dr Vardy and Dr Tannock reported on-going studies which indicate that multiple cytokines are elevated in subjects who have been treated for colorectal and breast cancer, in the absence of recurrence of disease, but that the levels were not higher in subjects who had received chemotherapy. There is emerging evidence that cytokine levels might relate to deficits in cognitive function [53].

genetic factors

Dr Ahles described potential genetic polymorphisms that might increase risk for chemotherapy-induced cognitive changes. One published study has reported an association between the E4 allele of apolipoprotein E (associated with risk for Alzheimer's disease and poorer cognitive outcomes following insults to the brain) and poorer cognitive performance in long-term survivors of breast cancer and lymphoma [54]. He proposed that genetic polymorphisms related to efficiency of the blood-brain barrier (e.g. differential expression of MDR-1) and the functioning of cytokines (e.g. polymorphisms of IL-6), neurotransmitters (e.g. COMT), and DNA repair mechanisms (e.g. XRCC1) might also be important [22].

International cognition and cancer task force

The second workshop led to the formation of the International Cognition and Cancer Task Force (ICCTF). The ICCTF is comprised of a multidisciplinary group of health professionals and patient advocates. The mission of the ICCTF is to advance understanding of the impact of cancer

and cancer-related treatment on cognitive and behavioral functioning in adults with nonCNS cancers.

A critical development from the Venice workshop was the formal establishment of an infrastructure to stimulate the growth of collaborative studies. A Steering Committee (see appendix) was formed that was charged with the responsibility of organizing and participating in Working Groups that will help identify knowledge gaps and formulate guidelines to assist those conducting research in this area: they will be responsible for ensuring integration and dissemination of the recommendations of the Working Groups. A small group of thought leaders in the area of neuropsychology, psycho-oncology, and medical oncology as well as patient advocates agreed to participate on an Advisory Board (see appendix). This board will provide guidance to the Steering Committee and Working Groups, help to facilitate interinstitutional and multinational collaborations, identify scientific research opportunities, and assist in obtaining funding for future research.

The Working Groups were developed around salient issues for the study of cognition and behavior in cancer patients. At present there are six identified Working Groups focusing on issues related to (i) neuropsychological assessment, (ii) trial design, (iii) prevention, management and intervention for cognitive and behavioral dysfunction, (iv) clinical epidemiology and translational guidelines, (v) imaging, and (vi) animal studies. While the Steering Committee has been charged with the responsibility for promoting integration between groups, periodic (every 2–3 years) meetings of the ICCTF will provide an opportunity for the entire Working Group membership to participate and present developments in their focus area.

The ICCTF has the explicit aim to assist not only health care professionals interested in this area, but also patients and their caregivers by providing up-to-date information on research activities and how best to support patients who are concerned about cognitive function. This will be partially achieved by the establishment of an ICCTF web site providing relevant information for all stakeholders.

funding

Hurricane Voices Breast Cancer Foundation; Susan G. Komen Foundation; Sanofi-Aventis; Bristol-Myers Squibb; Pfizer (Canada).

acknowledgements

This workshop was held in Venice, Italy, on 17 and 18 October 2006.

appendix

International Cognition and Cancer Task force

Co-Chairs:
Sanne Schagen and Janette Vardy

Steering Committee:
Janette Vardy
Sanne Schagen
Jeff Wefel
Tim Ahles

Advisory Board:
Ian Tannock
Frits van Dam
Patricia Ganz
Jimmie Holland
Christina Meyer
+Patient Advocate

2006 Cognitive Workshop participants:

Ahles, Tim*
Alibhai, Shabbir*
Barton, Debra*
Beadle, Geoff*
Boogerd, Willem
Buwalda, Bauke*
Castellon, Steven
Cherrier, Monique*
Colantuono, Janet**
Collins, Barbara*
Correa, Denise*
Dhillon, Haryana
Galica, Jacqueline
Ganz, Patricia
Giffard, Benedicte
Green, Heather*
Gundy, Chad
Heaton, Robert*
Hurria, Arti
Jacobsen, Paul*
Joly, Florence*
Kohli, Sadhna
Kreukels, Baudewijntje*
Lacey, Rachel*
Laye, Sopie
Maruff, Paul*
Metzger, Richard*
Minisini, Alessandro*
O'Brien, Patricia**
Olmstead, Marion**
Poppelreuter, Martin*
Quesnel, Catherine*
Ruiter De, Michiel
Schagen, Sanne*
Schilder, Christien
Seigers, Riejanne
Shapiro, Jamie*
Silverman, Daniel*
Stuart-Harris, Robin*
Tannock, Ian*
Van Dam, Frits
Vardy, Janette*
Wagner, Lynne*
Wefel, Jeff*
Winocur, Gordon*

*Presenter
**Patient Advocate

references

1. Tannock IF, Ahles TA, Ganz PA, van Dam FS. Cognitive impairment associated with chemotherapy for cancer: report of a workshop. J Clin Oncol 2004; 22: 2233–2239.
2. Anderson-Hanley C, Sherman ML, Riggs R et al. Neuropsychological effects of treatments for adults with cancer: a meta-analysis and review of the literature. J Int Neuropsychol Soc 2003; 9: 967–982.
3. Jansen CE, Miaskowski C, Dodd M et al. A metaanalysis of studies of the effects of cancer chemotherapy on various domains of cognitive function. Cancer 2005; 104: 2222–2233.
4. Stewart A, Bielajew C, Collins B et al. A meta-analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer. Clin Neuropsychol 2006; 20: 76–89.
5. Falleti MG, Sanfilippo A, Maruff P et al. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. Brain Cogn 2005; 59: 60–70.
6. Vardy J, Rourke S, Tannock IF. Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. J Clin Oncol 2007; 25: 2455–2463.
7. Tchen N, Juffs HG, Downie FP et al. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. J Clin Oncol 2003; 21: 4175–4183.
8. Mar Fan H, Houédé-Tchen N, Yi Q-L et al. Menopausal symptoms and cognitive function in women following adjuvant chemotherapy for breast cancer: one and two year follow-up of a prospective controlled study. J Clin Oncol 2005; 23: 8025–8032.
9. Schagen SB, van Dam FS, Muller MJ et al. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer 1999; 85: 640–650.
10. Brezden CB, Phillips KA, Abdolell M et al. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol 2000; 18: 2695–2701.
11. Ahles TA, Saykin AJ, Furstenberg CT et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol 2002; 20: 485–493.
12. O'Shaughnessy JA. Effects of epoetin alfa on cognitive function, mood, asthenia, and quality of life in women with breast cancer undergoing adjuvant chemotherapy. Clin Breast Cancer 2002; 3 (Suppl 3): S116–S120.
13. Wieneke MH, Dienst ER. Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. Psychooncology 1995; 4: 61–66.
14. van Dam FS, Schagen SB, Muller MJ et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst 1998; 90: 210–218.
15. Wefel JS, Lenzi R, Theriault RL et al. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer 2004; 100: 2292–2299.
16. Bender CM, Sereika SM, Berga SL et al. Cognitive impairment associated with adjuvant therapy in breast cancer. Psychooncology 2005; 15: 422–430.
17. Scherwath A, Mehnert A, Schleimer B et al. Neuropsychological function in high-risk breast cancer survivors after stem-cell supported high-dose therapy versus standard-dose chemotherapy: evaluation of long-term treatment effects. Ann Oncol 2006; 17: 415–423.
18. Schagen SB, Muller MJ, Boogerd W et al. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. J Natl Cancer Inst 2006; 98: 1742–1745.
19. Jenkins V, Shilling V, Deutsch G et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Cancer 2006; 94: 828–834.
20. Wefel JS, Lenzi R, Theriault R et al. 'Chemobrain' in breast carcinoma?: a prologue. Cancer 2004; 101: 466–475.
21. Vardy J, Rourke S, Galica J et al. Cytokine levels in patients (pts) with localized colorectal cancer (CRC) after surgery and their relationship to fatigue and cognitive function. J Clin Oncol 2006; 24: (Abstr 3623).
22. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 2007; 7: 192–201.
23. Carey CL, Woods SP, Gonzalez R et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol 2004; 26: 307–319.
24. Heaton RK, Grant I, Butters N et al. The HNRC 500–neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. J Int Neuropsychol Soc 1995; 1: 231–251.
25. Taylor MJ, Heaton RK. Sensitivity and specificity of WAIS-III/WMS-III demographically corrected factor scores in neuropsychological assessment. J Int Neuropsychol Soc 2001; 7: 867–874.
26. Heaton RK, Temkin N, Dikmen S et al. Detecting change: a comparison of three neuropsychological methods, using normal and clinical samples. Arch Clin Neuropsychol 2001; 16: 75–91.
27. Tuxen MK, Hansen SW. Neurotoxicity secondary to antineoplastic drugs. Cancer Treat Rev 1994; 20: 191–214.
28. Troy L, McFarland K, Littman-Power S et al. Cisplatin-based therapy: a neurological and neuropsychological review. Psychooncology 2000; 9: 29–39.
29. Saykin AJ, Ahles TA, McDonald BC. Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. Semin Clin Neuropsychiatry 2003; 8: 201–216.
30. Dietrich J, Han R, Yang Y et al. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents *in vitro* and *in vivo*. J Biol 2006; 5: 22.
31. Barton D, Loprinzi C. Novel approaches to preventing chemotherapy-induced cognitive dysfunction in breast cancer: the art of the possible. Clin Breast Cancer 2002; 3 (Suppl 3): S121–S127.
32. Joseph JA, Denisova N, Fisher D et al. Age-related neurodegeneration and oxidative stress: putative nutritional intervention. Neurol Clin 1998; 16: 747–755.
33. Ahles TA. Do systemic cancer treatments affect cognitive function? Lancet Oncol 2004; 5: 270–271.
34. Fillit HM, Butler RN, O'Connell AW et al. Achieving and maintaining cognitive vitality with aging. Mayo Clin Proc 2002; 77: 681–696.
35. Stemmer SM, Stears JC, Burton BS et al. White matter changes in patients with breast cancer treated with high-dose chemotherapy and autologous bone marrow support. AJNR Am J Neuroradiol 1994; 15: 1267–1273.
36. Inagaki M, Yoshikawa E, Matsuoka Y et al. Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. Cancer 2007; 109: 146–156.
37. Yoshikawa E, Matsuoka Y, Inagaki M et al. No adverse effects of adjuvant chemotherapy on hippocampal volume in Japanese breast cancer survivors. Breast Cancer Res Treat 2005; 92: 81–84.
38. Saykin AJ, McDonald BC, Ahles TA et al. Alterations in brain activation during working memory in patients with breast cancer: Relation to treatment modality, cancer status and task performance. 13th Annual Meeting of the Organization for Human Brain Mapping. Chicago, IL. Neuroimage 2007; 36 (Suppl 86).
39. Silverman DH, Dy CJ, Castellon SA et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5–10 years after chemotherapy. Breast Cancer Res Treat 2007; 103: 303–311.
40. Saykin AJ. Altered brain activation following systemic chemotherapy for breast cancer: interim analysis from a prospective study. J Int Neuropsychol Soc 2006; 12: 131.
41. Ferguson R, McDonald BC, Saykin AJ, Ahles TA. Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. J Clin Oncol 2007; 25: 3866–3870.
42. Kreukels BP, Schagen SB, Ridderinkhof KR et al. Electrophysiological correlates of information processing in breast-cancer patients treated with adjuvant chemotherapy. Breast Cancer Res Treat 2005; 94: 53–61.
43. Kreukels BP, Schagen SB, Ridderinkhof KR et al. Effects of high-dose and conventional-dose adjuvant chemotherapy on long-term cognitive sequelae in patients with breast cancer: an electrophysiologic study. Clin Breast Cancer 2006; 7: 67–78.
44. Winocur G, Vardy J, Binns MA et al. The effects of the anti-cancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. Pharmacol Biochem Behav 2006; 85: 66–75.
45. Reiriz AB, Reolon GK, Preissler T et al. Cancer chemotherapy and cognitive function in rodent models: memory impairment induced by cyclophosphamide in mice. Clin Cancer Res 2006; 12: 5000 author reply 5000–5001.

46. Macleod JE, Deleo JA, Hickey WF, Ahles TA. Cancer chemotherapy impairs contextual but not cue-specific fear memory. Behav Brain Res 2007; 181: 168–172.
47. Seigers R, Schagen SB, Beerling W et al. Long-lasting suppression of hippocampal cell proliferation and impaired cognitive performance by methotrexate in the rat. Behav Brain Res 2007 In press.
48. Lee GD, Longo DL, Wang Y et al. Transient improvement in cognitive function and synaptic plasticity in rats following cancer chemotherapy. Clin Cancer Res 2006; 12: 198–205.
49. Rzeski W, Pruskil S, Macke A et al. Anticancer agents are potent neurotoxins *in vitro* and *in vivo*. Ann Neurol 2004; 56: 351–360.
50. Scheibel RS, Valentine AD, O'Brien S, Meyers CA. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. J Neuropsychiatry Clin Neurosci 2004; 16: 185–191.
51. Capuron L, Ravaud A, Dantzer R. Timing and specificity of the cognitive changes induced by interleukin-2 and interferon-alpha treatments in cancer patients. Psychosom Med 2001; 63: 376–386.
52. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer 2005; 104: 788–793.
53. Vardy J, Booth C, Pond GR et al. Cytokine levels in patients (pts) with colorectal cancer and breast cancer and their relationship to fatigue and cognitive function. J Clin Oncol 2007; 25 (Suppl 18): (Abstr 9070).
54. Ahles TA, Saykin AJ, Noll WW et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psychooncology 2003; 12: 612–619.