International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer

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It has become increasingly apparent that cytotoxic drugs given systemically for non-CNS tumours might have cognitive side-effects, but many fundamental questions require further elucidation, and large samples from several institutions are needed. Two working groups brought together by the International Cognition and Cancer Task Force (ICCTF) developed recommendations for a core set of neuropsychological tests, common criterion for defining cognitive impairment and cognitive changes, and common approaches to improve the homogeneity of study methods. These recommendations will improve research design and facilitate study combinations, between-study comparisons, and meta-analyses, which will allow more accurate estimates of incidence, severity, individual risk factors, and causes of cognitive problems associated with chemotherapy for non-CNS tumours.

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Introduction

Cognitive problems are widely accepted as a possible consequence of brain irradiation or of intrathecal or intraventricular chemotherapy for CNS disease. An increasing number of neuropsychological studies show that cytotoxic drugs given systemically for non-CNS tumours might also have cognitive side-effects.[1–28] Human imaging and animal studies support a neurobiological basis for these effects, and unveil possible underlying mechanisms.[29–41]

With the increasing incidence of cancer and increasing use of chemotherapy drugs to treat different types of cancer, many cancer survivors could have cognitive deficits, which negatively affect quality of life and daily functioning, and are therefore an important concern. In this clinical context, the study of cognitive deficits in patients with non-CNS cancer is an important target. Increasing recognition of cognitive side-effects of systemic chemotherapy for non-CNS tumours has led to more effort worldwide to design studies that will further our knowledge of chemotherapy-associated cognitive deficits. Many fundamental questions require further elucidation, such as the incidence, time course, domains, and functional effect of cognitive dysfunction, as well as risk factors and mechanisms underlying these cognitive changes.

Studying cognitive dysfunction associated with chemotherapy is challenging, because cognitive deficits can be present before the start of treatment,[15,16,21,23,26,28] some combinations of cytotoxic drugs might be more likely to adversely affect cognitive functioning,[1,10,12,19] and not all patients are equally affected by the same chemotherapy regimen.[1,2,7–9,11–13,16,17,19–22,26,27] Moreover, estimates vary widely for the number of patients diagnosed with non-CNS tumours who experience cognitive deficits after treatment. This variance could be partly due to the use of different neuropsychological tests between studies, and different reference data and performance cutoffs for classifying test results. Neuropsychological studies have shown cognitive dysfunction in 13–70% of patients receiving chemotherapy.[1,2,7–9,11–13,16,17,19–22,26,27] Memory, processing speed, and executive function seem to be most vulnerable to adverse effects of chemotherapy.[42,43]

Wide variation in the frequency of observed cognitive decline stresses the need for studies with larger sample sizes. Larger studies would make it more feasible to accurately identify specific treatments (modalities, regimens, dosimetry, and timing) and patient characteristics (age, cognitive reserve, genetic risk factors, comorbid conditions, and other cancer-related symptoms) that constitute risk factors for cognitive decline. In-depth knowledge about specific neurotoxicity signatures of different therapies, and information on the long-term course of cognitive problems are sparse. Currently, several institutions individually undertake small studies. As a result, it takes many years for knowledge of chemotherapy-related cognitive dysfunction to progress. Most research on cancer-related cognitive deficits is still at an early phase, so large-scale studies are crucial to reach a breakthrough, and investigators need to pool and coordinate their efforts.

The International Cognition and Cancer Task Force (ICCTF) was founded in 2006 to provide a starting point for joint initiatives between international researchers and clinicians, to optimise progress in understanding cancer-therapy related cognitive dysfunction.[44] A specific goal of the ICCTF is to create research recommendations and guidelines to increase the homogeneity of study methods.[45] These guidelines will help to improve research design and facilitate between-study comparisons and meta-analyses, which will allow patients and professionals to make more accurate estimates of incidence, severity, individual risk factors, and causes of cognitive and behavioural dysfunction. Studies in this area are often done in a multidisciplinary setting. The research team can include neuropsychologists, psychologists, and collaborators with expertise in the type of cancer and treatment of interest (eg, oncologists or nurses). Depending on the research questions, experts in imaging, genetics, or biomarkers might also be a part of the team.

This review summarises the recommendations made by ICCTF working groups that were charged with the responsibility of generating suggestions about study design issues and neuropsychological assessment. The guidelines are for studies investigating cognitive function in human beings, as assessed by formal neuropsychological testing. By suggesting a minimum set of tests to be included in neuropsychological studies and criteria for the definition of cognitive impairment or change, as well as considerations that should be taken into account when designing a study, a better appreciation of the problem can be reached. Additional ICCTF working groups are planned to address issues associated with prevention, management, and intervention for cognitive and behavioural dysfunction, clinical epidemiology and translational guidelines, imaging outcomes, and animal studies. The goal of these recommendations is to translate knowledge into clinical application, to prevent and intervene against cognitive symptoms, and to ensure that accurate clinical data will guide future research.

Study design

Study design is mainly determined by the research question. The ideal research design to examine the effect of treatment would be a double-blind, randomised, placebo-controlled, prospective, longitudinal trial, with baseline cognitive assessments before treatment and long-term follow-up. However, since this is not feasible, most cognitive studies should be observational (with the exception of intervention studies), and include appropriate control groups to help to delineate the effect of a treatment on cognitive function.

Longitudinal versus cross-sectional studies

The ICCTF strongly recommends that longitudinal studies with repeat assessment be done whenever possible, to assess changes in cognitive function. Cross-sectional, post-treatment only studies with appropriate comparison groups might be useful for exploratory analysis, hypothesis generating, and for proof-of-concept trials, with findings confirmed longitudinally. However, interpretation of the results of these studies is limited, because group differences (eg, between patients exposed or not exposed to chemotherapy) do not necessarily reflect changes caused by chemotherapy.

Pretreatment cognitive performance

Results of longitudinal studies often show that 20–30% of patients had lower than expected cognitive performance before treatment.[15,16,21,23,26,28] Therefore, pretreatment cognitive assessments are recommended for these studies. For most tumour sites, these assessments would be done after surgery but before adjuvant therapy. For patients receiving neoadjuvant treatment (eg, for locally advanced rectal or breast cancer) baseline assessments should be done before the treatment under investigation. A presurgical assessment might be needed to address some research questions; however, this can be logistically difficult.

So far, it is unclear whether lower than expected pretreatment cognitive performance is due to adverse effects of the cancer itself, or to other, unidentified factors. Pretreatment impairment does not seem to be explained by factors such as depression, anxiety, or fatigue.[15,16,21] It could be that the adverse effects of cancer manifest themselves in vulnerable individuals, and these individuals are the most likely to show cognitive changes associated with cancer treatments; however, this possibility requires additional examination.

Control groups

Many patients receive multiple anticancer treatments; therefore, we are often studying the cognitive effect of combined treatments. For example, women with breast cancer can have several treatments that include surgery, chemotherapy (often with several drugs), radiation, endocrine therapies, and molecular targeted therapies. In theory, the relative effects of a particular treatment, such as chemotherapy, could be established if appropriate assessment timepoints and comparison groups were available (eg, patients who receive the same ensemble of treatments with or without chemotherapy). However, because of clinical treatment practices, the ideal comparison groups might not exist for the particular type of cancer or treatment of interest.

For most research questions, the ICCTF recommends several control groups—disease specific and healthy controls (both local controls and published normative data)—who undergo the same cognitive assessments in the same timeframe as the group of interest. This approach can help to establish whether cognitive impairment is present, and whether apparent changes in cognitive function are due to practice effect (ie, change over time associated with familiarity with the assessment rather than true improvement) or are secondary to the cancer itself, treatment, or both. In a non-randomised study, the disease-specific group is likely to consist of patients with the same cancer who receive a different anticancer treatment.

Patient populations

The patient population selected will depend on the research question. Choice of exclusion criteria becomes a balance between interpreting cognitive changes as due to treatment (excluding all other conditions or medications that could possibly affect cognitive functioning) and generalisability (including patients and controls who have typical comorbidities, such as hypertension and diabetes or are on common medications). A common dilemma is whether to exclude patients who are currently taking or have taken antidepressant medication, particularly selective serotonin-reuptake inhibitors (SSRIs). Depression and SSRIs have been inconsistently shown to affect cognitive performance.[46,47] Primary-care physicians often prescribe

SSRIs to patients who are feeling stress, who might not meet diagnostic criteria for depression, or for hot flashes.

Sample size and cooperative group studies

Single institutions can have difficulty accruing enough patients for a study to have the power necessary to make comparisons among treatment regimens. One solution is to design a multi-institutional study to accrue large numbers of patients in a timely manner. Selection of institutions with neuropsychologists interested in the cognitive effect of treatments would allow for a large neuropsychological battery and good quality control of the data.

Another option is to do research within the context of cooperative group studies. With this approach, large numbers of patients who meet similar inclusion and exclusion criteria are randomised to standardised treatments. A disadvantage is that these studies often accrue by many institutions enrolling a few patients each. Obtaining neuropsychological assessments and maintaining quality control of the data are challenges. However, neuropsychologists have done several such studies as part of the Radiation Therapy Oncology Group trials, as well as other cooperative groups, consortia, and sponsored trials, and these studies can serve as a model.

Neuropsychological assessment

Several considerations were taken into account when recommending which cognitive domains to assess and which specific neuropsychological tests to include, for researchers planning studies of the cognitive sequelae of cancer and treatment in adults with non-CNS tumours. First, objective tests remain the gold standard for measuring cognitive function. Self-reported complaints (ie, patient-reported outcomes) have not been validated as a means to assess cognition, and research shows a stronger association between subjective complaints of cognitive dysfunction and mood and fatigue, than between subjective complaints and objective tests of cognitive function.[16] Second, the cognitive domains to assess were recommended based on research findings. Studies done so far of the cognitive effects of chemotherapy show a frontal subcortical profile with the following domains mainly affected: learning and memory, processing speed, and executive function (eg, more complex aspects of attention). Tests with adequate sensitivity to measure these domains were chosen. Adequate psychometric properties were required, including test–retest reliability, the tests had to be suitable for multinational application, and alternate forms should be available. Frequent use of a test in the specific area of research being investigated, and use of these measures by other relevant consortia or cooperative groups, were also considered.[48,49]

Recommended tests

The following tests, which measure learning and memory, processing speed, and executive function, were selected: Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination.[50–54]

Learning and memory are crucial domains to assess, since longitudinal studies show objective cognitive impairment and decline in addition to subjective complaint by patients. The HVLT-R has adequate psychometric properties, six alternate forms, and has been translated into several languages (eg, English, Dutch, Spanish [for Spain], French [for France], Italian, and German), available through Psychological Assessment Resources, Inc. The TMT has adequate psychometric properties, is not language dependent, and the instruction set has been translated into several languages. The test measures psychomotor speed and aspects of executive function, which, in longitudinal studies, are often impaired at the time of diagnosis and are shown to decline. The COWA is a measure of speeded lexical fluency, which requires aspects of executive function; it has adequate psychometric properties and has one alternate form. The COWA (as opposed to the fluency test using the F-A-S letter set[55]) was developed by choosing letters that correspond to specified word frequencies in the English lexicon. A similar word-frequency approach has been taken to choose letter stimuli for several other languages, making this measure adaptable to multinational studies.

There was also interest in including additional measures of working memory (executive function, complex attention) in the assessment battery, based on clinician experience and subjective patient complaints. A separate test of working memory (eg, Auditory Consonant Trigrams,[56] PASAT [Paced Auditory Serial Addition Test],[57] Brief Test of Attention,[58] and WAIS-III Letter-Number Sequencing[59]) was not included in the suggested core battery of tests, since none of the available measures meets all the criteria outlined above. Investigators are encouraged to supplement the core battery with additional tests of working memory capacity, based on their own preferences.

Analytical methods

Three contributing factors to the wide variability in the reported incidence of cognitive impairment in cancer survivors include use of different neuropsychological tests, different criteria for defining cognitive impairment or cognitive change, and different comparison groups (eg, local healthy controls *vs* published healthy controls [normative data]). We did not intend to create diagnostic criteria for cognitive impairment after cancer and cancer treatment, and our proposed classification guidelines should not be interpreted as such. The guidelines are recommended to increase between-study interpretability. For studies in which the statistical method is incompatible with this classification approach, researchers are encouraged to describe their data in such a way that the classifications can be applied.

***Panel*: Considerations for analysing longitudinal data**

- Use of psychometrically matched, alternate forms is encouraged whenever feasible.
- Use of a prespecified Reliable Change Index (RCI) to determine change in cognitive function.[63-65]
- Regression-based approaches are also appropriate and might be more sensitive to changes in cognitive function over time.[65-67]
- Longitudinal modelling techniques are available. Growth curve, growth-mixture modelling, or linear mixed-effects models can be applied to assess effects at group and individual levels simultaneously.
- Analyses at the individual level have allowed researchers to identify predictors for the at-risk subgroup, and to estimate the prevalence of cancer and therapy-related cognitive decline.

Researchers are encouraged to present results of the core tests separately, to facilitate cross-study comparisons.

Recommended criteria to assess cognitive impairment

A combined, stepwise approach that specifies the cut-point for determining impairment in individual tests, and includes a battery-wide method to establish the expected frequency of abnormality when using several measures, is preferred. For example, the following method could be used to establish the frequency of cognitive impairment: first, find the number of patients with two or more test scores at or below –1·5 SDs from the normative mean (or the mean score of an appropriate control group), or the number of patients with a single test score at or below –2·0 SDs from the mean, or both; then, assess whether the frequency of cognitive impairment with the battery of measures exceeds expectation for use of several measures, by comparing the obtained frequency data with the probability curves, or the equation provided by Ingraham and Aiken,[60] or both. Investigators are encouraged to report data on the frequency of impairment for each test; the number of patients showing impairment on one, two, three, etc, tests; and the most common patterns of impairment. As the size of the test battery may influence the number of abnormal test results obtained, it is crucial to consider this when interpreting these data. Ingraham and Aiken[60] provide one means to consider the influence of multiple tests. Another method, that has been used to assess cognitive impairment at a given moment in time, is the Global Deficit Score (GDS).[61] The GDS is an actuarial approach that weights the number and severity of below-average scores in a battery, and therefore ignores scores in the average range or better. We do not recommend this approach to longitudinally monitor changes in cognitive function, since declines from a higher level to the average range will be ignored.

Search strategy and selection criteria

The International Cognition and Cancer Task Force (ICCTF) brought together experts in cancer and cognition to develop recommendations and guidelines to increase the homogeneity of study methods. A working group on study design and on neuropsychological assessment drafted potential guidelines that were presented at the ICCTF meeting in Amsterdam in 2008. After discussion, members of the two working groups reached consensus on the recommendations.

Recommended criteria to assess change in cognitive function

Detailed techniques and methods are available to help minimise practice effects and measurement error, which is especially important in uncontrolled trials where analyses of differential practice effects are not possible.[60] The use of alternate forms does not necessarily eliminate all confounding due to practice effects; however, alternate forms of tests such as the HVLT-R were studied in the context of serial testing, and there was no significant evidence of residual practice effects.[62] The panel shows recommendations for analysing longitudinal data.

Discussion

Although research examining cognitive changes associated with non-CNS cancer and treatment has increased in the past several years, more investigation is needed to provide the following: an accurate estimate of the incidence and course of post-treatment cognitive decline; the relative cognitive effects of various chemotherapy regimens and the contribution of endocrine therapy and radiation; risk factors for cognitive decline; mechanisms (biological and psychological) underlying cognitive changes; and the effect of cognitive changes on a patient's daily life and ability to function. Larger samples collected from many institutions will help to answer these questions. One of the goals of the ICCTF working groups is to provide suggestions for a core set of neuropsychological tests, a common criterion for defining impairment, and common methodological approaches for combining data across studies. These are not intended to be prescriptive guidelines, but a collaborative approach for leveraging data collected at several sites to answer important questions that cannot be answered through single-institution studies. Further, creation of a collaborative network could lead to multicentre studies to examine genetic factors that increase vulnerability to cognitive decline, and imaging studies at institutions that have the capability. This initiative is not meant to interfere with or restrict studies by individual investigators, or reports based on data collected at their institutions. Additionally, we recognise that policies for authorship and access to combined datasets need to be established. We hope that the recommendations formulated by ICCTF working groups

are an initial step toward developing a large source of data to accelerate progress in the area of cancer and cognition.

Contributors

All authors contributed to the design, development, writing, and editing of the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

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