Review Article

Impact of Cancer and Its Treatments on Cognitive Function: Advances in Research From the Paris International Cognition and Cancer Task Force Symposium and Update Since 2012

Florence Joly, MD, PhD, Bénédicte Giffard, PhD, Olivier Rigal, MD, Michiel B. De Ruiter, PhD, Brent J. Small, PhD, Martine Dubois, PhD, Johan LeFel, PhD, Sanne B. Schagen, PhD, Tim A. Ahles, PhD, Jeffrey S. Wefel, PhD, Janette L. Vardy, MD, PhD, Véronique Pancré, PhD, Marie Lange, PhD, and Hélène Castel, PhD

Departments of Clinical Research Unit and Medical Oncology (F.J., M.L.), Centre François Baclesse; CHU Côte de Nacre (F.J.); U1086 INSERM-UCBN Cancers & Préventions (F.J., M.L.); UMR-S1077 (B.G.), UNICAEN, Normandie Université; U1077 INSERM (B.G.); Ecole Pratique des Hautes Etudes, UMR-S1077 (B.G.); CHU de Caen, U1077 (B.G.), Caen; Service des Soins de Support and Département d'Oncologie Médicale (O.R., J.L.), Centre Henri-Becquerel, Rouen, France; Department of Psychosocial Research and Epidemiology (M.B.D.R., S.B.S.), Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; School of Aging Studies (B.J.S.), University of South Florida, Tampa, Florida, USA; INSERM U982 (M.D.,H.C.), Laboratory of Neuronal and Neuroendocrine Communication and Differentiation, DC2N, Astrocyte and Vascular Niche, Biomedical Research Institute (IRIB), University of Rouen, Mont-Saint-Aignan, France; Neurology Service (T.A.A.), Memorial Sloan-Kettering Cancer Center, and Weill Medical College of Cornell University, New York, New York, USA; Section of Neuropsychology (J.S.W.), Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA; University of Sydney (J.L.V.), Sydney, and Concord Cancer Centre, Concord Hospital, Concord, New South Wales, Australia; and NorthWest Canceropole (V.P.), CNRS−UMR 8161−Institut de Biologie de Lille, Lille, France

Abstract

Context. Although cognitive impairments have been identified in patients with non−central nervous system cancer, especially breast cancer, the respective roles of cancer and therapies, and the mechanisms involved in cognitive dysfunction remain unclear.

Objectives. To report a state-of-the-art update from the International Cognitive and Cancer Task Force conference held in 2012.

Methods. A report of the meeting and recent new perspectives are presented.

Results. Recent clinical data support that non−central nervous system cancer per se may be involved in cognitive dysfunctions associated with inflammation parameters. The role of chemotherapy on cognitive decline was confirmed in colorectal and testicular cancers. Whereas the impact of hormone therapy remains debatable, some studies support a negative impact of targeted therapies on cognition. Regarding interventions, preliminary results of cognitive rehabilitation showed encouraging results. The methodology of future longitudinal studies has to be optimized by a priori end points, the use of validated test batteries, and the inclusion of control groups. Comorbidities and aging are important factors to be taken into account in future studies. Preclinical studies in animal models highlighted the role of cancer itself on cognition and support the possible benefits of prevention/care during chemotherapy. Progress in neuroimaging will help specify neural processes affected by treatments.

Conclusion. Clinical data and animal models confirmed that chemotherapy induces direct cognitive deficit. The benefits of cognitive rehabilitation are still to be confirmed. Studies evaluating the mechanisms underlying cognitive impairments using advanced neuroimaging techniques integrating the evaluation of genetic factors are ongoing. J Pain Symptom Manage 2015;50:830−841.

Key Words

Cancer, chemotherapy, cognition, elderly, neuroimaging

Address correspondence to: Florence Joly, MD, PhD, Département d'Oncologie Médicale, Recherche Clinique, CHU Côte de Nacre et Centre François Baclesse, BP 5026, 3 Av. Général Harris, 14076 Caen Cedex 05, France. E-mail: f.joly@baclesse.fr

Accepted for publication: July 6, 2015.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2015.06.019

Introduction

It is now accepted that cancer treatments may induce cognitive impairments, particularly in the domains of memory, concentration, information processing speed, and executive functions. Cancer-related cognitive impairment was first reported in the context of brain irradiation. More recently, research largely focused on neurotoxicity associated with chemotherapy, leading to the general concept of "chemofog."[1] Most of these studies have been conducted in young patients with localized breast cancer, and it appears that a subgroup experiences, in most cases, subtle or moderate cognitive dysfunction.[2] The impact of hormone therapy on cognition is not well understood.[3,4]

Although it is acknowledged that chemotherapy is a risk factor for cognitive deficits, there are still many unresolved questions. These issues include the characterization of subgroups at risk, the impact of cancer per se and of other factors like aging or comorbidities, the specific effects of different treatment modalities, and the optimal way to improve the management of cognitive impairment in routine practice. Furthermore, there are still important gaps in our knowledge and understanding of the mechanisms implicated in cognitive disorders.

Over the past 10 years, the International Cognitive and Cancer Task Force (ICCTF) has organized a biannual multidisciplinary meeting involving neuropsychologists, clinical and experimental psychologists, medical oncologists, imaging experts, basic science researchers, nurses, and allied health professionals, with the aim of sharing state-of-the-art knowledge regarding the impact of cancer and its treatments on cognitive function. The first meetings mainly focused on cognitive changes secondary to adjuvant chemotherapy for breast cancer.[5,6] Based on a multidisciplinary working group approach, in 2011, the ICCTF published recommendations to harmonize the methodology of studies evaluating cognitive function in patients with cancer.[7] In 2012, the ICCTF symposium held in Paris aimed to update the advances in research on cognition in non−central nervous system (CNS) cancers. During this meeting, new aspects of research were presented, including important advances in basic science (various preclinical animal models) and in human brain imaging based on magnetic resonance imaging (MRI) and positron emission tomography (PET). In addition, translational research, including the role of different inflammatory biomarkers, was presented. The aim of this article is to summarize the main topics and advances presented during the symposium that have since been published and to review the new perspectives that have emerged since the Paris meeting.

Report From the 2012 ICCTF Paris Meeting

How to Improve Methodological Aspects of Cognitive Clinical Trials?

The development of well-designed clinical trials assessing cognitive function in patients with cancer was an important issue and long considered as critical by all clinical and neuropsychological professionals in the field. Past and current discussions focused on ways of improving some methodological aspects in studies assessing cognition. First, it was recommended to define an a priori cognitive end point and to use a validated neuropsychological battery of tests.[7] Thus, different methods of statistical analysis had to be debated. B. Small demonstrated that traditional statistical methods, such as those based on repeated analysis of variance, have important limitations, especially in the case of missing data and unequally spaced measurement intervals. He proposed alternative models more suitable for analysis of longitudinal studies evaluating cognitive function. Random effects models allow longitudinal data to be processed more flexibly and innovatively, with few penalties and less impact from missing data, and the ability to take into account practice effects.[8,9] Other models such as growth mixture models[10] allow testing hypotheses regarding the presence of subgroups of patients, some of whom may be experiencing a precipitous decline. Latent change score models enable investigators to link changes across multiple variables and to test hypotheses regarding whether changes in one aspect (e.g., biological markers) may precede or follow changes in another aspect (e.g., behavioral tasks).[11] Finally, a presentation of integrative data analysis[12,13] received considerable attention from scientists. Similar to a meta-analysis, but with raw data, information from multiple samples (which is often the situation in cognitive studies) could be combined into a single data analysis, despite the fact that all outcomes may not be measured using the same instruments. This type of analysis is expected to increase statistical power and generalizability of results.

Another debate, conducted by Collins et al.,[14] concerned the choice of appropriate control groups and led to the suggestion of choosing suitable published test-retest norms for all neuropsychological tests (that may require local controls) even if it remains a challenge. She showed significantly different rates of cognitive decline in patients treated with chemotherapy according to the control method used. In addition, the choice of local controls is also challenging. Healthy controls can be well matched for key demographic variables, but possible confounding factors such as constitutional risk factors, psychological distress, and disease-related cognitive changes, if