
4. AXIS 4 : “CANCER AND NEUROSCIENCES”

Steering committee: F. Joly, H. Castel-Gandolfo, B. Giffard

The aim of this new research axis created by CNO in 2007 was to bring together clinicians and researchers on original interdisciplinary projects at the interface between neuroscience and cancer which would have an impact on patient care. The development of an innovative programme to assess the influence of the illness and its treatments on patients' cognitive functions was therefore started in 2007 with the objectives of 1) investigating the onset of cognitive problems in patients potentially induced by cancer and cancer treatments on a longitudinal basis; 2) evaluating and understanding of the mechanisms and physiopathology of these problems using a neuropsychological approach and with the help of animal models, and 3) developing tools that would help define patients' cognitive complaints and testing these nationally.

The existence of cognitive impairment has been described recently in cancer. This new area of research in oncology addresses an actual clinical situation, as patients often complain of problems with their memory, concentration and thought processing capacities, which has a negative impact on their quality of life, either during or after treatment, in particular with chemotherapy treatments. These memory problems are sometimes also noted soon after the diagnosis before treatment. There are several factors which may explain these cognitive complaints. The stress induced by the cancer diagnosis can lead to cognitive impairment and in view of the current state of knowledge regarding the links between emotion and cognition, it is difficult to distinguish the effects specifically related to treatment from those linked to anxiety symptoms. Moreover, very little research has been carried out into the age factor, even though this factor tends to have a negative impact on cognition and patients aged 65 or over account for a large proportion of the cancer patient population. These patients therefore constitute a group particularly at risk for developing cognitive problems during treatment.

There is no standardised method for neuropsychological evaluation of the patients' complaints, the clinical studies that have been conducted to date (mostly in young women having undergone chemotherapy for breast cancer) differ widely in methodology and few of them have been longitudinal.

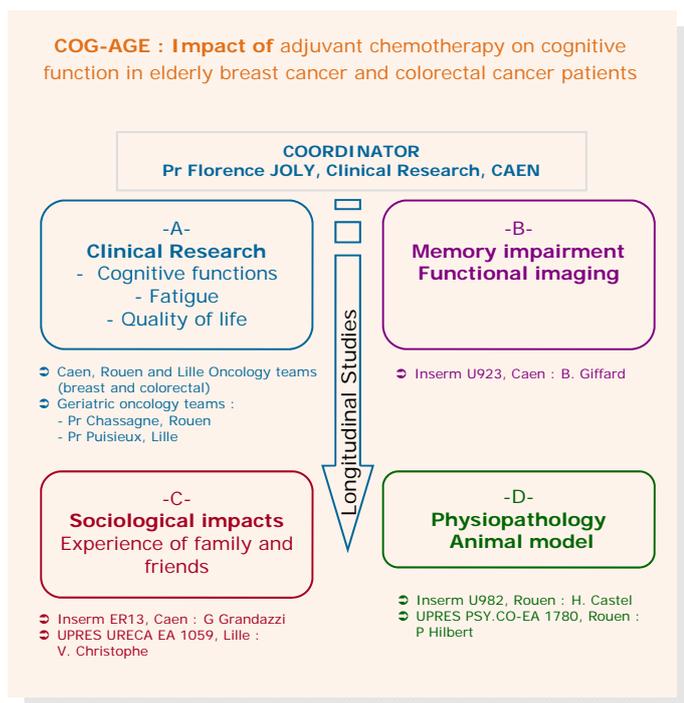
Some preliminary studies have implicated a direct toxic effect on the brain of chemotherapy treatments in the onset of cognitive deficits (primarily deficits of memory, executive functions and thought processing speed). These deficits could be caused by a set of psycho-sociological changes (stress associated with the announcement, change in social status, the person's questioning of their identity). Certain biological changes may also be implicated to some extent in cognitive problems, such as anaemia, increased cytokine secretion or genetic disturbances. The physiopathology and mechanism of onset of these problems are not clearly identified. The prefrontal gyrus and parahippocampal gyrus may be implicated. Animal models may be a useful approach for a more specific investigation into whether or not there is a direct casual link between the patient's drug treatments and the emergence of the cognitive impairments observed during their follow-up.

A. Key developments

Although several clinical studies have been published (conducted primarily in women with breast cancer), to date the real impact of cancer treatments (chemotherapy or targeted treatments) and of the cancer itself on cognitive function, the actual effects linked with cancer pathology and the nature of the impairments and associated mechanisms are poorly understood, due to *i*) the absence of a standardised test battery, *ii*) insufficient longitudinal clinical trials, and *iii*) the absence of standardised animal models for investigating these mechanisms.

It was to address these issues that a multidisciplinary working group was formed in 2007 at the initiative of Prof. F. Joly, (medical oncologist, Centre F. Baclesse, Caen), the first and only one of this cancer area of research its kind both in France and internationally. The group involves several of CNO's sites (Caen, Rouen, Lille and Brussels) and is made up of medical oncologists trained in clinical research, researchers specialising in health, social sciences and psychology, biologists and neuroscientists for the cerebral imaging and understanding of the cellular and molecular mechanisms.

Starting in 2007, the group developed an initial ambitious multicentre and multidisciplinary longitudinal project designed to investigate the specific impacts of adjuvant chemotherapy in elderly patients having undergone treatment for breast cancer or colorectal cancer, covering both patients and animal models studies (COG-AGE).



By encouraging and setting up regular working meetings and organising a first national seminar on “Cancer and Cognitive Function” in January 2008 in Trouville, CNO was able to build on the original group, which expanded to include clinical and research staff at the Rouen, Caen, Lille and Brussels sites. The group was also quickly identified at the international level by ICCTF (*International Cognition and Cancer Task Force*) and took part in task forces and in writing guidelines for neuropsychological assessments in oncology.

B. Original Projects

The subject of the flagship multidisciplinary project for Axis 4 was the evaluation of the impact of adjuvant chemotherapy on cognitive function in elderly patients having undergone treatment for breast or colo-rectal cancer (COG-AGE, coordinated by F. Joly). Adjuvant chemotherapy is being proposed more and more frequently to elderly patients, in spite of the low level of expected clinical benefits,

By setting up national and international networks on this theme, the group was able to validate a self-questionnaire (Fact-cog) written in French and designed to assess the cognitive problems experienced by patients. The questionnaire was drawn up and tested in collaboration with the team led by David Cella at CORES (*Center on Outcomes, Research and Education, Chicago, USA*). The analysis of the results has been completed and publication is currently underway.

This initial programme was the starter for other projects to begin underway. These are *i)* national multicentre pilot clinical projects supported by the pharmaceutical industry, involving investigating the impacts of hormone therapy and new targeted therapies on cognitive function; *ii)* dealing with the complaints described by patients followed up in oncology departments and their expectations in terms of specific management of their cognitive problems, and finally *iii)* clinical evaluation of the therapeutic effects of neuroprotective agents or neurostimulants on cognitive impairment in patients having undergone radiotherapy for brain metastases.

With the help of the logistical and financial support provided by Cancéropôle Nord-Ouest, the group’s efforts in establishing this network have focused on:

- Acquiring expertise, whilst working towards gaining recognition for skills in this new research field, including in the context of answering calls for proposals;
- Recruiting doctorate and post-doctorate students and training them in this area. Three PhD (*doctorat*) students and one post-doctorate student have recently joined the group;
- Organising multicentre clinical trials involving neuropsychologists in oncology departments (including setting up the appropriate infrastructures).

with few backgrounds among elderly patients (the majority of patients who have taken part in clinical trials have been under 65 years of age). This project began properly in 2009 with support from PHRC 2008 and CNO. The aims of COG-AGE were *i)* to investigate the frequency and severity of memory problems induced by adjuvant chemotherapy in elderly patients with breast or colorectal cancer and their impact on quality of life using a multicentre,

longitudinal study and including a geriatric oncology approach and a psychosociological survey of friends and family (G. Grandazzi and V. Christophe); *ii*) to identify the mechanisms involved in these memory problems, depending on whether they are induced by the chemotherapy or by psychosociological changes, using a neuropsychological approach (coordinated by B. Giffard), and *iii*) to understand the physiological and biological mechanisms implicated in cognitive functional impairment, primarily with the aid of an animal behavioural model (coordinated by H. Castel). Thanks to an array of different partnerships, some of the findings have already been presented. In July 2010, 65 patients were enrolled in the clinical longitudinal study.

Some preliminary results for the baseline cognitive state of the patients were presented to ICCTF in New York in 2010 (Dr Giffard) and to the 2nd meeting of the Federation of the European Societies of Neuropsychology (Amsterdam 2010). Baseline cognitive function of the first 30 elderly patients with breast cancer was tested before any treatment was initiated and was compared with the average in the general population. A significant percentage of the patients with localised breast cancer had some cognitive impairment before they had even received any chemotherapy (compared with the general population, 38% more women had significant concentration problems unrelated to anxiety level or depression). A correlation was however found between the objectively measured impairment and the subjectively reported problems, a relationship of which until then there had been little evidence in the literature. These results reinforce the hypothesis that the cancer event alone can cause the onset of cognitive impairment, and memory problems in particular. The correlation found between subjective and objectively measured problems could be explained by the age effect, as some of the patients had comparatively greater impairment of cognitive function at baseline and were thus more susceptible to developing problems during chemotherapy in relation to younger patients. In terms of methodology, these results also confirmed the necessity of a baseline measurement in order to evaluate the specific impact of adjuvant chemotherapy on cognitive function.

Some interesting original conclusions were able to be derived from the animal studies. The team led by H el ene Castel recently developed an animal model designed to determine the direct impact of chemotherapy on cognitive function on the basis of age. This study showed that long-term administration of 5-fluorouracil (5-FU), either alone or in combination with oxaliplatin, does not alter anxious or depressive behaviours nor learning or spatial memory performance in young and elderly mice. However, mice treated with 5-FU showed medium-term behavioural flexibility impairment and overreaction to new events. Metabolic activity in the brain is modified in the frontal and hippocampal structures involved in the cognitive flexibility circuits. Co-administration of glucose with the 5-FU, either alone or in combination with oxaliplatin, protects the animals from the cog-

nitive impairment caused by chemotherapy in the behavioural model. *In vitro*, the harmful effect of treatments on the survival and proliferation of neural stem cells is also partly offset by co-administration of glucose or insulin. This research will be continued in CNO's 2011-2014 plan. These findings were presented at AACR 2009, ASCO 2010, ICCTF 2008 and 2010 and CNO's 2009 and 2010 science days. The publication, which is currently being finalised, will be submitted to the *Journal of Clinical Oncology*.

In addition, the interest that patients have in the effects of the treatments and of the illness were assessed by means of a memory survey (COG-MEMO) which was developed and conducted in 551 patients undergoing treatment in the regional cancer centre (CLCC) outpatient clinics in Caen, Rouen and the Jules Bordet institute in Brussels. This study confirmed that the impact of the treatments on their cognitive function is a major issue for patients. Over 80% of the patients questioned considered this a priority issue in the evaluation of treatment side effects. Forty percent of patients complained of cognitive problems and two thirds of patients would be in favour of specific remedial cognitive workshops. Following on from the findings of this research, it is planned to study the impact of remedial cognitive workshops on quality of life and improvement of cognitive function in patients complaining of cognitive problems (see CNO 2011-2014 Plan).

The impetus provided by the COG-AGE study has also led to the launch of a pilot longitudinal clinical trial to assess the impact of targeted therapies on quality of life and cognitive function in patients undergoing treatment for metastatic kidney cancer (COG-ANGIO). This study addresses a clinical situation in which patients have sometimes major side effects such as fatigue that could be a state of lethargy, together with concentration difficulties and poor attention span. The frequency and severity of these problems described frequently by patients have never been examined in specific clinical studies. This multicentre prospective clinical research project, which aims to enrol 120 patients, is currently underway, thanks to support from the pharmaceutical industry in collaboration with Institut Gustave Roussy, H opital Pominpou and Strasbourg University Hospital. In August 2010, 45 patients were enrolled. This is the first study to date to evaluate the impact of targeted therapies on cognitive function in patients undergoing treatment for kidney cancer. Some preliminary results from the first 20 patients were presented to ESMO in September 2010 (Dr S. Noal).

C. Networking and events

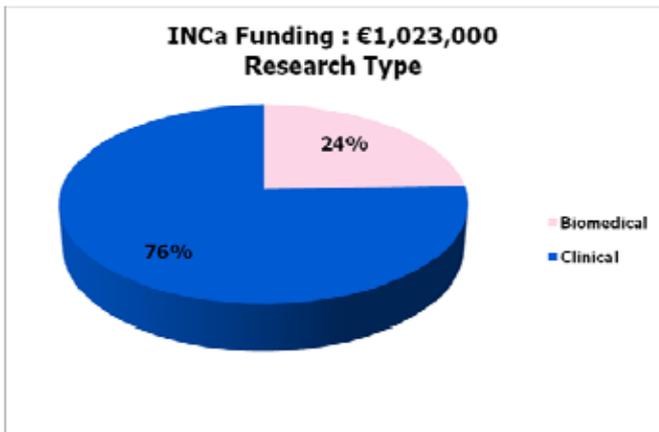
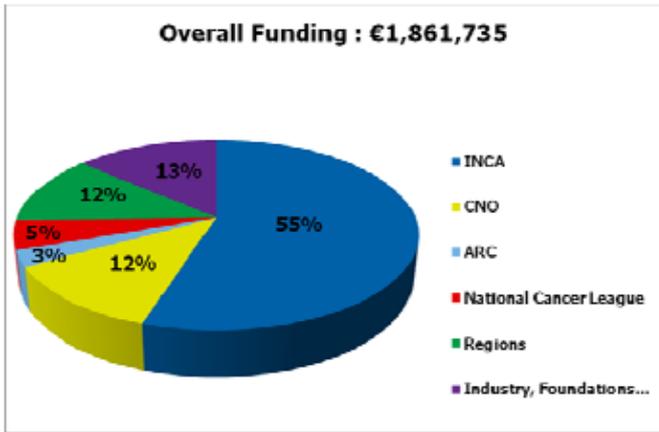
The teams belonging to this axis meet twice a year for working seminars (June 24th and November 24th 2008, June 26th and October 30th 2009, March 25th 2010) and two national symposiums on “Cognitive Function and Cancer” were organised in Trouville in January 2008 and March 2010 (*see programmes in the appendix 7*).

These provided an opportunity to obtain an up-to-date picture of the problems encountered in the different situations, to tackle methodological difficulties and to propose research projects, in the presence of internationally renowned experts invited by CNO (Dr Janette Vardy from Sydney in 2008 and

Dr Barbara Collins from Ottawa in 2010). Collaboration with Cancéropôle Grand-Est (CGE) Quality of Life research platform has also got underway. Florence Joly, the joint coordinator for this axis, is a member of the technical committee for this platform. CNO's Axis 4 aims to position itself as France's leading organisation for the subject “Impact of cancer and cancer treatments on cognitive function” and will continue with its dynamic events programme by organising national symposiums every 2 years and organising the ICCTF international symposium in Paris in march 2012.

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More than half of the support provided by CNO for axis 4 went towards personnel costs with two-year funding for a post of engineer and one year's funding for a postdoctorate student for the development of the animal behavioural model, plus part-time funding for a neuropsychologist for the patient testing and joint funding for the first year of a PhD on quality of life. Support for emerging projects was also provided, for the clinical trial, functional MRI scans and the development of the animal model.

11 projects were funded for the period 2007-2010 by the various organisations funding cancer research in France, broken down as follows:

- ⇒ INCa (*Institut national du cancer* – National Cancer Institute): 4 projects, including 3 PHRCs (hospital-based clinical research programme) and 1 open topic in biomedical research (*see appendix 4*).
- ⇒ ARC (*Association pour la Recherche sur le Cancer* – Cancer Research Association): 1 project).
- ⇒ Haute Normandie, Basse Normandie, Nord and Picardie Regional cancer leagues: 3 projects and 1 PhD (*doctorat*) research grant.
- ⇒ Pharmaceutical industry: 2 projects.
- ⇒ Inter-regional cancer centres (CLCCs): 1 project.

This axis will have had 9 publications based on these research projects to its credit between 2007 and 2010 (*see appendix 5*).

