



Cognitive complaints in breast cancer patients treated with chemotherapy: a reality?

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Memory and attention dysfunction is a common complaint among cancer survivors, named “chemobrain”, which can be reported during and even several years after treatment. These disorders have a negative impact on patients’ quality of life (1) and can disturb ability to work (2). Recent studies assessed self-reported cognitive function in cancer patient cohorts, mainly in breast cancer women, and showed that 46% to 60% of survivors had cognitive complaints (3-5). However, these studies did not use a validated questionnaire specifically constructed to assess cognitive complaints.

Generally, patients who report cognitive complaints do not systematically have objective cognitive impairment assessed within neuropsychological tests. These two measures of cognition provide complementary information and perceived cognitive dysfunctions correlate strongly with psychological factors (6).

The article by Janelins *et al.* (7) explored specifically cognitive complaints in a cohort of cancer patients. Cognitive difficulties before and after chemotherapy were assessed in breast cancer survivors recruited from community oncology clinics (mean age 53 years old; 22–81 years old). The authors followed 581 patients and 364 healthy controls over 1 year. Cognitive complaints were assessed by the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) (8). The published data were part of a prospective longitudinal trial which also assessed objective cognitive functioning.

The authors hypothesized that perceived cognitive difficulties would be more prevalent among patients than healthy controls and these difficulties would persist

longitudinally. Furthermore, age, education, race, menopausal status, anxiety and depression at baseline would be associated with persistent cognitive complaints which could also be observed with control of these variables. Finally, they hypothesized that patients treated with anthracyclines would experience more cognitive difficulties than those who had not received them.

Results showed that before chemotherapy, breast cancer patients had significantly more cognitive complaints than healthy controls. Patients also expressed more anxiety and fatigue than controls. After adjustment, notably on psychological factors, a trend of more complaints was only observed on the patient group, reinforcing the fact that cognitive complaints are linked to emotional state.

During the follow-up, although the FACT-Cog scores of healthy controls did not change, breast cancer patients had a significantly higher increase of cognitive complaints than healthy controls on the four FACT-Cog subscales and on the total score, from pre- to post-chemotherapy.

Patients were more likely to express an increase of significant clinical cognitive complaints than were healthy controls from pre-chemotherapy to post-chemotherapy (45.2% *vs.* 10.4%) and from pre-chemotherapy to 6 months after treatment (36.5% *vs.* 13.6%). However, from post-chemotherapy to 6 months, the proportion of patients who expressed an increase of significant clinical cognitive complaints increase was not significantly different to that of controls (18.4% *vs.* 11.5%). Six months after chemotherapy, results of patients suggested a certain recovery from cognitive complaints but without return to pre-treatment

level. Therefore, the results of this study suggest that perceived cognitive disorders are mainly related to diagnosis of cancer and cognitive complaints increase mainly during the chemotherapy treatment period.

Anxiety and depression scores, cognitive reserve, and menopausal status were the main predictors of lower FACT-Cog scores. Chemotherapy regimens (with anthracyclines), radiation therapy or hormonal therapy were not significantly associated to FACT-Cog total score and age was associated with the subscale Perceived Cognitive Abilities (PCA) of the questionnaire.

The strengths of this study are to assess cognitive complaints longitudinally in a large sample of patients recruited from community oncology clinics (who provide a representative sample) and in a control group with a validated questionnaire. The FACT-Cog questionnaire has the advantage of being specifically constructed to assess cognition in cancer patients. It consists of four subscales (Perceived Cognitive Impairments, Comments From Others, Perceived Cognitive Abilities and Impact on Quality of Life) and a total score can be calculated with the version two of the questionnaire used in the study. The last subscale enables to assess the impact of the cognitive difficulties on quality of life, which is very important to assess if cognitive difficulties have a significant impact on daily activities and on work. This information is crucial to propose specific management to reduce difficulties (e.g., cognitive rehabilitation).

Cognitive complaints assessment could be a more sensitive measure than performances on cognitive tests to show cognitive modifications (9), notably in patients with high cognitive reserve or those who could compensate their difficulties and did not have apparent disorders on objective cognitive tests (10).

Furthermore, the authors also assessed anxiety, depression and fatigue, usually related to cognitive complaints. If anxiety and fatigue were assessed with dedicated questionnaires, depressive symptoms were captured by only one item on the fatigue scale, which may have underestimated the relation between cognitive complaints and depression. Fatigue, which can be related to cognitive complaints (11,12), was not considered as a covariate in the study of Janelins *et al.* and could influence FACT-Cog scores.

Otherwise, contrary to the initial hypothesis, age was a significant predictor only for PCA scale. In a study we conducted in elderly breast cancer patients treated with chemotherapy, we also found a relation between age and PCA subscale (13). This subscale seems to be sensitive to age effects.

The majority of previous cohort studies showed that to have been treated with chemotherapy was associated with cognitive complaints compared to patients who had

not received this treatment (3-5). Janelins *et al.* observed that patients reported greater cognitive difficulties than healthy controls. The choice of the control group is a key point to assess the specific impact of cancer and of cancer treatments. Studies should include a group of patients with experience of cancer who have not received chemotherapy, such as a group treated with radiotherapy, to precisely assess the impact of chemotherapy on cognition.

Besides, the hypothesis that anthracyclines would lead to more cognitive difficulties was not verified in this study.

In the article that accompanies this editorial, breast cancer patients were followed up only 6 months after chemotherapy: what happened after? Previous results on cognitive complaints reported contradictory results. If one showed that about 5 years post-diagnosis, 46% of cancer survivors reported cognitive dysfunctions (5), other studies reported that the majority of survivors maintained good long-term self-reported cognitive function up to 7 years after treatment initiation (3) or that the proportion of survivors with cognitive complaints was comparable to normative data of 7-9 years follow-up after breast cancer surgery (14). In this way, considering heterogeneous results of cognitive complaints after cancer treatments in previous cohort studies (3,5,14), a long term follow up of more than one year would have been interesting.

If most of the patients seemed to improve FACT-Cog scores from the end of chemotherapy to 6 months follow-up, 18% of patients kept on increasing cognitive complaints. Unfortunately, characteristics of this group were not identified. A previous study showed that a subgroup of older breast cancer survivors (8%), assessed at baseline and follow-up annually for up to 7 years, had an accelerated decline, mainly associated with comorbidity and frailty (3).

The publication of the objective cognitive functioning assessment based on neuropsychological tests will be interesting, notably to show if objective cognitive disorders are also observed and which cognitive domains are impaired.

In summary, perceived cognitive difficulties after chemotherapy are frequent in breast cancer patients and these difficulties seem to decrease 6 months after treatment. Even if "chemobrain" seems to be a transient problem, some women could have difficulties at longer term which could impact the ability to work. Anthracyclines did not seem to induce more cognitive complaints than protocol without them. Future research is needed to identify the profile of patients at higher risk of cognitive complaints. Early assessment of cognitive complaints and their management could help to facilitate the return to work of young women, avoid potential repercussions on adherence to oral treatments and on autonomy in older patients.

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