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# Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study

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**Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study**

The objective of this study is to investigate if changes in cognitive functions can be recognised in patients undergoing chemotherapy for breast cancer. Forty women with breast cancer and without depression underwent cognitive evaluation before and after 6 months of chemotherapy; emotional evaluation was performed before and after 1, 3 and 6 months of chemotherapy. Self-reported cognitive deficit evaluation was included. Global cognitive functioning before starting chemotherapy was good. After 6 months of treatment there was a significant decline in some cognitive functions, particularly involving the attention subdomain. Objective cognitive deficit resulted independent from the emotional status. On the contrary, self-perceived mental dysfunction was unrelated to the objective cognitive decline, but it was associated with depression and anxiety. Breast cancer chemotherapy can induce domain-specific cognitive dysfunction. Patients' self-perception of mental decline is unrelated to objective cognitive deficit. Breast cancer patients negatively judge their cognitive performances if they have a negative emotional functioning.

*Keywords:* cognitive dysfunction, chemotherapy, breast cancer, neuropsychological assessment.

## INTRODUCTION

An increased number of people with cancer complain about cognitive problems (Vardy *et al.* 2007). Many cancer patients complain 'chemo fog' or 'chemo brain', which is the cognitive change that patients attribute to chemotherapy (Raffa *et al.* 2006). On the other hand, there is also an increased risk of cognitive impairment in cancer patients who have had no chemotherapy exposure (Hermelink *et al.* 2007). Thus, assessment before and after

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chemotherapy is necessary in order to establish if cognitive deficit is caused by the exposure to chemotherapy or to other factors.

Particular relevance has been given to chemotherapy-induced cognitive changes in the mnemonic and attention domains (Wefel *et al*. 2004). Cognitive impairments in the oncological population can be related to several mechanisms such as the direct effects of illness and/or chemotherapies on the Central Nervous System (CNS), hormonal effects and/or psychological factors, such as mood depression (Ahles & Saykin 2007).

It is well known that stressful experiences, such as a disease, can inhibit hippocampal neurogenesis, strictly related to memory, perhaps through a modified expression of GABA-A receptors (Earnheart *et al*. 2007). A long-term stress-related reduced neurogenesis can induce mood depression through serotonin under-transmission (Meeter *et al*. 2006). Global slowing is a major cognitive deficit in depression that can mimic selective impairments in more effortful task conditions (Pardo *et al*. 2006). A growing body of data supports the hypothesis that mood depression should be considered as a systemic disease (Torta 2006). Not only neurotransmitters, but also hormonal and immunological systems are involved in the pathogenesis of major mood depression. For example, the hypothalamus-pituitary-adrenal axis is overactivated (Barden 2004) and a decrease in oestrogen level induces mood depression. Proinflammatory cytokines play an important role in modulating mood disturbances within CNS (Schiepers *et al*. 2005). Also neurotrophic factors (such as brain-derived neurotrophic factor) are involved in the pathophysiology of mood disorder, possibly protecting the CNS against stress-induced neuronal damage (Hashimoto *et al*. 2004).

The aim of our study is to investigate if changes in cognitive function can be recognised in patients undergoing chemotherapy for breast cancer and if emotional aspects related to cancer diagnosis may also play a role on cerebral functioning.

## MATERIALS AND METHODS

### Study population

This study was approved by the Ethic Committee and all patients gave their written informed consent. Forty-five consecutive women with breast cancer, aged between 18 and 65, undergoing an adjuvant or neoadjuvant treatment with potentially neurotoxic chemotherapeutic drugs were recruited. Exclusion criteria were: previous treatment for cancer, pre-existing depressive or psychotic disorders, previous use of any psychoactive drug (with the exception of benzodiazepines), life expectancy below 18 months, being pregnant or nursing a child. Women started endocrine adjuvant treatment after the end of chemotherapy (after T3); thus endocrine treatment was not a confounding factor. Five of the 45 patients dropped out: one participant refused to continue the treatment, 3 women did not complete all assessments for disease recurrence and one because of worsened health conditions. Thus, 40 women entered the study. Table 1 shows the demographic characteristics of the sample population and the performed treatment.

### Assessments

Premorbid intelligence was estimated using a language-related test, the TIB (Brief Intelligence Test) (Sartori *et al*. 1997), which is the Italian version of the National Adult Reading Test (NART).

**Table 1.** Demographic characteristics of the sample population and treatment performed for breast cancer

| | | | |
|---|---|---|---|
| Age (years) | Mean | 51 | |
| | Range | 38–65 | |
| | SD | 7.81 | |
| Educational level | Elementary school | 4 | 10% |
| | Junior high school | 17 | 42.5% |
| | High school | 13 | 32.5% |
| | University | 6 | 15% |
| Surgery | Breast-conserving surgery plus radiotherapy | 22 | 55% |
| | Mastectomy | 16 | 40% |
| | Neoadjuvant chemotherapy only | 2 | 5% |
| Chemotherapy | FEC | 17 | 42.5% |
| | FEC+T | 18 | 45% |
| | A+T | 5 | 12.5% |
| Hormonal therapy (5 years treatment) | None | 14 | 35% |
| | Tamoxifen | 16 | 40% |
| | Aromatase inhibitors | 10 | 25% |

FEC, cyclophosphamide, epirubicine, 5-fluorouracil; FEC+T, cyclophosphamide, epirubicine, 5-fluorouracil, docetaxel; A+T, doxorubicine, paclitaxel.

**Table 2.** Results of cognitive tests before (T0) and after 6 months of chemotherapy (T3)

| Test | T | Mean score | SD | *P* value (T0→T3) |
|---|---|---|---|---|
| MMSE | 0 | 27.76 | 1.33 | **0.002** |
| | 3 | 26.77 | 2.15 | |
| Attentive Matrices | 0 | 50.99 | 6.17 | **0.022** |
| | 3 | 48.70 | 6.53 | |
| Digit Span Forward | 0 | 5.57 | 1.06 | 0.052 |
| | 3 | 5.20 | 1.38 | |
| Trail Making Test* | | | | |
| Part A | 0 | 45.50 | 17.75 | **0.032** |
| | 3 | 41.50 | 14.77 | |
| Part B | 0 | 95.62 | 33.65 | 0.293 |
| | 3 | 100.25 | 41.91 | |
| Phonemic Word Fluency | 0 | 33.05 | 12.67 | 0.520 |
| | 3 | 31.97 | 10.95 | |
| Short Story-immediate recall | 0 | 8.05 | 2.49 | 0.676 |
| | 3 | 7.85 | 2.92 | |
| Short Story-delayed recall | 0 | 7.51 | 2.56 | 0.636 |
| | 3 | 7.27 | 2.96 | |
| Rey Auditory Verbal Learning Test-immediate recall | 0 | 40.79 | 9.39 | 0.318 |
| | 3 | 42.41 | 10.37 | |
| Rey Auditory Verbal Learning Test-delayed recall | 0 | 8.44 | 2.74 | 0.870 |
| | 3 | 8.52 | 2.68 | |
| Raven's Progressive Matrices | 0 | 118.32 | 12.43 | 0.311 |
| | 3 | 120.32 | 10.56 | |

*Time in seconds.
MMSE, Mini-Mental State Examination.

Cognitive function was examined using 10 neuropsychological tests (Raven 1938; Reitan 1958; Folstein *et al.* 1975; Spinnler & Tognoni 1989) (Table 2). The tests were selected for reliability, validity and availability of Italian standards, as well as for their sensitivity to measure mild cognitive impairment in repeated assessment during a brief period of time (6 months), limiting any practice effect. The cognitive assessment was performed before starting chemotherapy (T0) and after 6 months (immediately after the end of chemotherapy) (T3). A battery of five emotional tests was used to investigate the patients' emotional status (Karnofsky *et al.* 1948; Montgomery & Asberg 1979; Zigmond & Snaith 1983; Fayers *et al.* 1999; Grassi *et al.* 2005) at baseline (T0), during chemotherapy treatment [after 1 (T1) and 3 (T2) months from the first evaluation] and at the end of chemotherapy (T3). An evaluation of the self-perception of cognitive deficit was included (Wagner *et al.* 2004). Correlations between cognitive and emotional evaluations were analysed. The patients' test results were compared with test norms.

### Statistical analysis

Statistical analysis was carried out using SPSS for Windows. We used Paired-Sample *t*-tests to compare cognitive performances made at T0 and T3. We carried out repeated ANOVA measures to compare the emotional assessments (T0–T1–T2–T3) with the Bonferroni correction. The correlation between cognitive and emotional tests has been estimated with Pearson's index of correlation. The level of significance was established at 0.05.

## RESULTS

### Cognitive assessment

Comparing the pre-treatment evaluation (T0) with the one done after chemotherapy (T3), the mean scores showed a significant worsening in the global cognitive functioning and in the visual selective attention while processing speed significantly improved during time, probably due to practice effect. Table 2 summarises the results of cognitive tests.

#### *Mini-Mental State Examination (MMSE) (Folstein* et al. *1975)*

It measures global cognitive function. It is divided into six sections: space–time orientation, memory, attention and calculation abilities, recalling, language and visual-constructional abilities. A worsening was shown between T0 (mean score 27.8) and T3 (mean score 26.8) ($P = 0.002$). Furthermore, the percentage of patients with a score under-

the-mean increases after chemotherapy (19.5% at T0 versus 30.8% at T3); 42% of the women did not show any change.

*Attentive Matrices (Spinnler & Tognoni 1989)*

It investigates visual-selective attention (the ability to focus on specific information while ignoring others less relevant). There was a significant decrease after 6 months of treatment ($P = 0.022$). At the end of chemotherapy the percentage of women with an unsatisfying score is 15.4% in comparison with 9.8% at T0.

*Trail Making Test A e B (Reitan 1958)*

It is a test of visual-conceptual and visual-motor tracking that explores mental flexibility, spatial planning, shifting ability, processing speed and motor speed. It is divided in two parts, A and B. The processing speed measured by the part A significantly improved after 6 months of treatment ($P = 0.032$), as the time spent to complete it progressively decreases at the different evaluations (from 45.50 s at T0 to 41.50 s at T3); this is probably due to practice effect. On the contrary, mental flexibility measured by part B of this test, much more difficult and less influenced by training, only showed a worsening trend (mean time 95.6 s at T0 versus 100.2 s at T3).

All the other tests [Digit Span Forward (Spinnler & Tognoni 1989), which provides measures of short-term memory and sustained attention (the ability to keep attention) by forward repetitions of series of numbers; Phonemic Word Fluency (Spinnler & Tognoni 1989), which assesses the ability to find words from the internal lexicon; Short Story (Spinnler & Tognoni 1989), which evaluates verbal learning by an immediate recall task and a delayed recall task; Rey Auditory Verbal Learning Test (Spinnler & Tognoni 1989), which establishes both the short- and long-term skill to retain and learn 15 words following interpolated activity; Raven's Progressive Matrices (Raven 1938), which examine global intelligence and analytic, spatial and reasoning abilities] did not show any significant difference at the cognitive assessment before and after chemotherapy.

**Emotional assessment**

*Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith 1983)*

It is a 14-item self-reporting scale that provides scores on two parameters, depression and anxiety. Both self-reported anxiety and depression levels were within normal range at T0. Analysing differences during the study period, anxiety levels significantly decreased from baseline assessment (mean score 7.12) to T3 (mean score 4.74) ($P = 0.028$).

*Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg 1979)*

This scale, which is completed by physicians, evaluates mood depression. Scoring is based on a 6-point rating scale: reported sadness, apparent sadness, suicidal thoughts, pessimistic thoughts, inability to feel (anhedonia), lassitude, difficulty in concentration, loss of appetite, insomnia and psychic anxiety (inner tension). Higher score values suggest worse mood alteration. There was no significant difference before and after 6 months of chemotherapy, both in the individual items and in the total score.

*Mini-Mental Adjustment to Cancer (Mini-MAC) (Grassi* et al. *2005)*

This self-reported scale measures styles of coping with cancer. At baseline, the most frequent styles of coping were fatalism (21.6%), fighting spirit (23.6%) and avoidance of the illness (22%); hopelessness was reported only by 13% of women. Patients did not change their inner strategies of coping during the 6 months of study.

*European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (Fayers* et al. *1999)*

It is a cancer-specific, self-administered, structured questionnaire containing five functioning subscales (physical, role, emotional, cognitive and social functioning), nine symptom subscales (fatigue, pain, nausea, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and global health and quality of life items. In the functioning and symptom subscales higher scores suggest a worse condition. As expected, there was a temporary worsening of some physical functions during chemotherapy (T1 and T2), like dyspnoea, nausea and vomit, improving at the end of chemotherapy. Fatigue, pain and appetite loss were maximum after one month of therapy (T1): often at the beginning of treatment symptoms are emphasised by the emotional status. We observed a significant decrease in the item 'role functioning' (ability to make hard works or walk long distances) during chemotherapy (mean score 36.3 at T1 versus 35.1 at T0); this

**Table 3.** Correlation between the HADS anxiety and depression scores with the EORTC QLQ-C30 subscales

| | | | HADS | |
|---|---|---|---|---|
| | | | Anxiety | Depression |
| | | | *P* value | |
| EORTC subscales | Functioning | Physical | 0.01 | 0.01 |
| | | Role | 0.01 | 0.01 |
| | | Emotional | 0.01 | 0.01 |
| | | Cognitive | 0.01 | 0.01 |
| | | Social | 0.01 | 0.01 |
| | Symptoms | Fatigue | 0.01 | 0.01 |
| | | Nausea and vomiting | Not significant | Not significant |
| | | Pain | 0.01 | 0.01 |
| | | Dyspnoea | 0.01 | 0.05 |
| | | Insomnia | 0.01 | 0.01 |
| | | Appetite loss | 0.01 | 0.01 |
| | | Constipation | Not significant | 0.05 |
| | | Diarrhoea | 0.01 | 0.01 |
| | | Financial difficulties | Not significant | Not significant |
| | GH and QoL | Global health* | 0.01 | 0.01 |
| | | Quality of life* | 0.01 | 0.01 |

*Negatively related.
HADS, Hospital Anxiety and Depression Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire Core 30.

problem is solved at the end of chemotherapy, with a mean score of 29.8 at T3 visit ($P = 0.016$).

*Karnosfky Performance Status (Karnofsky* et al. *1948)*

It is a tool to assess cancer patients' functional integrity. It investigates four areas: personal care, daily activities, working activities, signs and symptoms related to the illness and to treatment. The patients showed stability across evaluations, maintaining good scores at each visit (96.7 at T0 and 96.3 at T3 on a scale from 0 to 100).

**Self-perception of cognitive deficit**

*Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog, version 2) (Wagner* et al. *2004)*

It evaluates the self-perception that women have of their cognitive deficit. It explores through 50 questions different domains: cognition (which includes mental shape, concentration, verbal and non-verbal memory and fluency), global functioning and the impact of the disease on the quality of life. Observing the mean of all the FACT-Cog scores, women did not believe to have important cognitive problems: the FACT-cog total score was 3.18, very close to 4 which indicates 'absence of the problem'. The perception of mental impairment by relatives was even less worrying, as the mean score in the FACT-cog outside observation is 3.3. There were no significant differences in the self-perception of cognitive deficit before and after treatment (T0 versus T3 evaluations). The self-perception of cognitive functioning did not correlate with the objective results at the cognitive assessment, while there was a strong correlation between the total FACT-Cog score and the emotional evaluation. In fact, the total mean score obtained at the FACT-cog was negatively related to the level of anxiety ($P = 0.01$) and to depression score ($P = 0.01$) resulting by HADS test and to the apparent ($P = 0.01$) and reported ($P = 0.01$) sadness evaluated by the MADRS test. There was also a negative correlation between the total FACT-Cog score and some items of EORTC QLQ-C30: physical functioning ($P = 0.05$), role functioning ($P = 0.05$), emotional functioning ($P = 0.01$), cognitive functioning ($P = 0.01$) and social functioning ($P = 0.05$) and fatigue ($P = 0.01$). On the contrary, it was positively related to the EORTC global health ($P = 0.05$) and quality of life ($P = 0.05$). In conclusion, the questionnaire FACT-Cog showed a lower score if there were higher levels of anxiety, depression and, in general, if there was a worse quality of life, highlighting a decreased self-consideration in these conditions.

**Correlations between cognitive and emotional evaluations**

From the analysis of correlations between emotional aspects and cognitive functions, objective cognitive deterioration seems to be independent from mood status. The only significant correlations were between the emotional assessment and the physical symptoms ($P < 0.01$)

(Table 3). There was a strong correlation between the HADS score of anxiety and depression and the EORTC QLQ-C30 subscales of physical symptoms (fatigue, appetite loss, pain, dyspnoea and insomnia) and emotional, cognitive and role functioning. On the contrary, we observed no correlation between mood and objective symptoms, like nausea and vomit which are strictly related to chemotherapy treatment.

## DISCUSSION

Studies on cognitive and emotional functioning in patients with cancer are often difficult to compare due to methodological problems. This study is a prospective one that includes an accurate pre-treatment assessment of women. Furthermore, beyond the emotional and cognitive evaluation, it includes an assessment of the self-perceived cognitive functioning. The major limit of our study is the small sample and the lack of a control group.

### Cognitive functions

The results of this study suggest that in women treated for breast cancer, chemotherapy induces a deterioration in some cognitive functions. We observed a decrease, after 6 months of chemotherapy, both in the global cognitive functioning and in the visual selective attention. Verbal skills, oral learning and short-term memory showed a non-significant worsening trend, whereas learning abilities and logical functions did not appear compromised. Processing speed significantly improved during time, probably due to practice effect. The negative effect of chemotherapy on some cognitive subdomains observed in our series is consistent with previous studies that highlight a subtle, though not always statistically significant, cognitive decline (Bender *et al*. 2006; Schagen *et al*. 2006; Stewart *et al*. 2008). On the contrary, other studies do not report cognitive impairment during chemotherapy (Jenkins *et al*. 2006).

Consistent with Bender, our data suggest that the mental deficit is domain-specific (Bender *et al*. 2006). On the contrary, other authors report a global worsening in all cognitive domains (Wieneke & Dienst 1995; Van Dam *et al*. 1998; Schagen *et al*. 1999). Our study includes a pre-treatment evaluation, which is essential to establish whether the deficits emerged after treatment or if they were already present before, as a consequence of cancer itself (false positives) (Ahles *et al*. 2007; Hermelink *et al*. 2007; Wefel *et al*. 2010). Wefel *et al*. (2010) reported a cognitive deterioration in 21% of women affected by non-metastatic breast cancer prior to adjuvant chemotherapy, especially in verbal learning and motor abilities, with a strong correlation with anxiety and depression levels. For this reason, Hermelink *et al*. (2007) suggested to replace the term 'chemobrain' with 'crisis brain'. Moreover, a decrease in cognitive performances in a patient 'high cognitive-functioning' could not be detected if the scores after the end of the chemotherapy still remain in the normality range (false negatives).

The decline in the visual attention subdomain described in this study is reported also by others (Schagen *et al*. 1999). Furthermore, many authors found a similar negative trend of mental flexibility, verbal learning, verbal memory and verbal skills (Wieneke & Dienst 1995; Schagen *et al*. 1999; Ahles *et al*. 2002; Wefel *et al*. 2004). All meta-analysis published on this topic confirmed a subtle, domain-specific cognitive deterioration after chemotherapy (Anderson-Hanley *et al*. 2003; Falleti *et al*. 2005; Jansen *et al*. 2005; Stewart *et al*. 2006).

In our study, the objective deterioration observed in the cognitive domains seems to be independent from the emotional status.

### Emotional status

As highlighted by Hurria *et al*. (2007), accurate emotional evaluation of the patients is very important. Many studies on this topic lack suitable controls on potential confounders such as depression, anxiety and fatigue. In the present study the emotional evaluation was performed before, during and after chemotherapy and women with pre-existing depression were excluded from the study to avoid bias. Due to the recent awareness of having a cancer, anxiety was the main feeling at first assessment, progressively decreasing during chemotherapy. This reduction can be due to a better understanding of the treatment steps and to the fact that the patient learns to face the illness.

Physical functioning is negatively affected by chemotherapy (Ahles *et al*. 2002). As predictable, some physical symptoms, like nausea and vomit, are treatment-related and generally disappear at the end of chemotherapy. As a consequence, women find more difficult making hard works or walking long distances during chemotherapy. High levels of anxiety and depression are associated, in our series, to more pessimistic evaluation of physical symptoms. Our findings concur with research (Hermelink *et al*. 2010) that found a substantial role of negative affectivity in the reporting of physical symptoms. The fatigue symptom, recently renamed Cancer-Related Fatigue Syndrome, is both a physical symptom (muscular weakness) and an emotional one (patients refer to lack motivation and to spend much more energy to execute functions that

before the illness were automatic) (De Jong *et al*. 2005). As reported in literature and confirmed by our data, fatigue is strongly related to high levels of anxiety and depression (Valentine & Meyers 2001).

### Self-perception of cognitive deficit

In our series, the self-perception of mental deficit seems unrelated to the objective cognitive decline, as demonstrated also by Shilling and Jenkins (2007). The lack of association between subjective and objective evaluations of cognitive functioning suggests that the group of patients who feel cognitively impaired is different from the group of patients who show impairment in cognitive tests (Hermelink *et al*. 2010). On the other hand, many studies have found an association of self-reported cognitive function with negative emotional status (Van Dam *et al*. 1998; Schagen *et al*. 1999; Shilling & Jenkins 2007; Hermelink *et al*. 2010). Our study confirms the association between the self-perceived cognitive dysfunction and the presence of anxiety and depression. However, it is unknown if the negative emotional status increases the reporting of cognitive symptoms or if existing cognitive problems lead to psychological distress (Pullens *et al*. 2010).

## CONCLUSION

This study suggests that breast cancer chemotherapy can induce cognitive dysfunction, involving especially the attention subdomain. The *objective* cognitive deterioration seems to be independent from the emotional status. On the contrary, the *self-perceived* cognitive dysfunction appears to be related to the presence of depression and anxiety. There is no association between cancer patients' self-perception of mental dysfunction and the objective cognitive decline. As a consequence, the self-perception of cognitive deficit can be considered as a pessimistic interpretation of cognitive functioning induced by treatment burden and negative emotional status regardless from the presence of neuropsychological compromise. Moreover, women with high levels of anxiety and depression tend to report more pessimistic evaluations of physical symptoms. Longer observation is needed to evaluate whether the decline in cognitive functioning is temporary or does persist over time.

## CONFLICT OF INTEREST STATEMENT

All authors disclose any financial and personal relationships with other people or organisations that could influence this work.

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The study has no sponsors.

## ETHICAL APPROVAL

This study was approved by the San Giovanni Battista Hospital of Turin (Italy) and University International Ethic Committee and all patients gave their written informed consent.

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