Longitudinal Evolution of Cognitive Function in Colorectal and Breast Cancer Survivors Treated with (Neo)Adjuvant Chemotherapy.

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Research Article
Abstract

Introduction & objectives:

Advances in early diagnosis and treatment are improving the long-term survival of patients with cancer. Cancer-related cognitive impairment (CRCI) is often reported as a long-term chemotherapy sequel. Improving the knowledge of CRCI may help to prevent, manage and identify risk factors. Our main goal is to assess the cognitive function evolution and determine the potential influence of chemotherapy in neurological decline.

Material and methods

We designed a prospective and longitudinal study of a colorectal and breast cancer patient cohort (n=62) and we assessed cognitive function evolution using a battery of 11 neuropsychological tests at three time points: baseline, post chemotherapy and 6 months after finishing chemotherapy. Sociodemographic features, quality of life, anxiety and depression status were recorded as well as their interplay with cognitive evolution.

Results

At baseline, 14.5% of the patients had cognitive dysfunction. Older age, low level of education, colorectal cancer and comorbidities were associated to initial cognitive damage. A total of 61.9% of patients presented a decline of scores in 4 or more tests from baseline to post chemotherapy assessment. This percentage decreased to 24.4% in the late follow up evaluation, showing an intra-patient recovery after chemotherapy. Verbal and visual memory is the domain most affected.

Conclusion

Our data suggest that cognitive function of cancer patients treated with chemotherapy may subtly but transiently decline during treatment, with most patients recovering their cognitive function over time. Further research is needed in this field as CRCI continues to impact on quality of life and mental well-being.

Introduction

Cancer-related cognitive impairment (CRCI)

Cancer is a major public health problem whose number of affected patients is expected to increase each year. Advances in early diagnosis and cancer treatment are improving the long-term survival of many patients diagnosed with this disease. Adjuvant chemotherapy is one of the most relevant factors for
improving survival rates in early stages diagnosis. However, there is growing concern about the sequelae that may remain after antineoplastic therapy or directly after diagnosis of a neoplasm. These scientific achievements impact not only in the rates of overall survival of cancer patients, also in the late toxicities related to treatments we can find in long-term survivors with different needs over the years. Late toxicities can negatively impact on quality of life and they could even lead to functional limitation in daily life and/or the work environment and psychosocial wellness (1–3).

Cognitive decline is one of the most frequently reported symptoms by cancer patients, also known as 'cancer-related cognitive impairment' (CRCI), ‘chemobrain’ or ‘chemofog’. CRCI has been increasingly recognized as a side effect of both cancer and cancer treatment throughout last years (4).

Studies in this area have mainly investigated CRCI in a post-chemotherapy setting and have suggested that the most affected neurological functions are short-term and working memory, executive functions, attention and processing speed. Nevertheless, subtle cognitive deficits across multiple domains have been described (5).

The depth, extent and duration of cognitive dysfunction, as well as, its potential reversibility is not well known. Some publications have reported that this condition is transitory and others suggest that the deterioration could continue up to 20 years later (6).

The frequency of CRCI varies widely between publications, estimating an incidence in 30% in patients prior to any therapy, up to 13-70% of patients receiving chemotherapy and in up to 75% of patients after treatment. Most studies have been performed among early breast cancer patients, and less frequently, colorectal cancer patients (7). This is in view of the fact that these are the two most common cancer subtypes with the best rates of survival. The incidence of cognitive decline within breast and colon cancer survivors is estimated around 21-58% and 46-56% respectively. However, in general only 15-25% of patients have objective cognitive changes (7, 8).

The discordance among subjective complaints and objective dysfunction is a difficult challenge to overcome and one of the factors that explain the complexity in estimating an accuracy incidence (9). Psychological factors could also influence these differences. Despite International initiatives such as International Cancer and Cognition Task Force (ICCTF), there is no definitive consensus regarding the neurocognitive tests to be performed or criteria for defining cognitive impairment in reported publications (10). These could help us to better understand the differences observed in the rate of incidence or the different features between studies. The real incidence or prevalence of cognitive disorders might be underestimated.

The etiology of CRCI is not well known and it is likely multifactorial with the participation of many potential mechanisms in its development. Factors directly related with the tumor or with the antineoplastic treatment have been suggested as being potentially involved in the development of cognitive dysfunction; such as proinflammatory state produced by the neoplasm per se, hormonotherapy or neurotoxicity of chemotherapy (11, 12).
CRCI is a growing health problem that affects thousands of cancer survivors. Also, CRCI represents a major concern of patients and impacts on their work and social networks (3). However, to date, the duration of CRCI, its reversibility, the cognitive areas most affected and other specific characteristics are not well defined.

The aim of this project is to study the cognitive evolution among breast and colorectal cancer patients and to assess the potential influence of adjuvant/neoadjuvant chemotherapy on neurological decline. We also intend to determine incidence, features and duration of CRCI, in order to improve the understanding of this health problem and consequently to be able to respond to it as a scientific community.

Materials And Methods

Study design

A prospective, longitudinal, observational study was designed. Patients diagnosed with colorectal and breast cancer receiving adjuvant/neoadjuvant chemotherapy, were recruited from Hospital Clínico Universitario Lozano Blesa in Zaragoza (Spain) between 2017 and 2019.

The project was designed according to the ethical principles of the Declaration of Helsinki, and, the approval of the regional ethics committee (CEICA record nº CP04/2016) was obtained. All participants provided written informed consent.

Patients included

To be included in the study, patients had to fulfill the following criteria: (i) 18-75 years of age diagnosed with early-stage breast cancer or colorectal cancer (CRC) (stages I to III), (ii) scheduled to receive neo- or adjuvant chemotherapy, either taxanes with or without anthracyclines for breast cancer or fluoropyrimidine with or without oxaliplatin for CCR, and (iii) able to understand the informed consent and neurological tests.

Patients were excluded if they have: (i) received prior treatment with chemotherapy or radiotherapy in the last 5 years, (ii) documented neuropsychiatric disorders that might result in poor cognitive abilities (e.g., Parkinson's disease, dementia, substance abuse, major depression), (iii) use of neuropsychiatric treatment or (iv) toxic abuse.

Study procedures

Demographic variables (age, sex, civil status and education level), medical information records (comorbidities, performance status (PS)) and medical oncological history (cancer diagnosis, chemotherapy regimen, dose and duration) were obtained before the initiation of the study.

Neuropsychological evaluation was collected at 3 time points: 1) baseline (M0) before the initiation of chemotherapy (from 4 weeks to 48 hours before); 2) post-chemotherapy (M1) after treatment completion
(from 1 to 4 weeks after completion) and 3) late follow-up (M2) at 6 months after finishing the chemotherapy treatment (from 24 to 30 weeks after completion).

At each point of assessment, patients have to complete 11 tests to evaluate different neurocognitive abilities: Rey Auditory Verbal Learning Test (RAVLT) (13, 14), Number sequencing, Letter-Number sequencing and Block design from Wechsler Adult Intelligence Scale III (WAIS-III) (15), Digit Span and Spatial Span from Wechsler Memory Scale (WMS-III) (16), Verbal fluency test (VFT) (semantic and phonetic) (17, 18), Visual Memory subtest PIEN from Barcelona Test (19), Stroop test (20, 21) and Trail Making Test (TMT A and B) (22–24).

The test battery was selected in order to explore the main subareas of cognitive function: verbal and visual memory, executive function (processing speed), psychomotor function (attention) and visuoconstructive function.

Health-related quality of life, anxiety, and fatigue were also assessed using Hospital Anxiety and Depression Scale (HADS) (25), FACT – B. Functional Assessment of Cancer Therapy – Breast, and FACT – C. Functional Assessment of Cancer Therapy – Colorectal (26, 27).

Cognitive functions, quality of life and mental wellness were evaluated using different tests as shown in Table 1.

All cognitive assessments were carried out by specialists in neurocognitive evaluation, in Spanish, and in the same spatial conditions at each time point.

**Statistical Analysis**

A descriptive analysis of all included variables in the study was performed. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as absolute values and percentages. Univariate linear regression models were used to study the association between clinical-demographic factors and cognitive dysfunction at baseline. The non-parametric Kruskall-Wallis test was used to study the difference in the evolution of neurocognitive test across the three time points. According to previous studies (Wefel et al), raw scores were converted into z scores (mean=0, SD=1) using published normative data adjusted for age, education, and gender. At each time point, patients were classified as having cognitive impairment if one out of the two following criteria was met: (1) z scores of \( \leq -1.5 \) for more than one test and (2) z scores of \( \leq -2.0 \) for just one test. The Mann–Whitney test was used to assess the difference in the number of impairment tests between patients with or without cognitive dysfunction. The threshold for statistical significance was defined as 0.05 (two-sided). No correction for multiplicity was performed, due to the exploratory character of the study, and no data imputation was used. The data analyses were carried out using R statistical software version 3.6.2.

**Results**

**Patient characteristics**
Between April 2017 and January 2019, a total of 105 patients were identified for the study, 62 patients met the eligibility criteria and were included in the study and 43 potential candidates were ineligible for enrollment (figure S1 reflects the reasons for exclusion).

At baseline, among the included population (n=62), median age was 55.5 years (range: 30-74 y), 51 were females (82.3%), 49 patients were married (79%) and 13 (21%) had other marital status (single, separate or widower). Regarding educational level, half of the patients had completed tertiary study. Tobacco consumption was present in 13 patients (21%) and alcohol consumption in 12 (19.4%). Most of the patients had some comorbidity at the time of inclusion (58.1%). Comorbidity data are shown in table S1 in the Supplementary Appendix.

Compared to 22 patients (35.5%) with colorectal cancer, a higher number of breast cancer patients were included, totalling 40 patients (64.5%). Among those diagnosed with breast cancer, 20 were treated with adjuvant chemotherapy and 20 with neoadjuvant chemotherapy. All the patients with colorectal carcinoma received adjuvant CT.

The drugs administered during treatment are listed in table S2 in the Supplementary Appendix.

In addition, 50% (77.5% of patients with breast carcinoma) received adjuvant radiotherapy. The adjuvant chemotherapy treatment was followed by hormone therapy in 26 (65%) of the patients with breast carcinoma. More sociodemographic features are summarized in table S3 in the Supplementary Appendix.

Clinical and demographic factors associated with greater cognitive dysfunction at baseline

Figure 1 shows the association between clinic-demographic factors and the level of cognitive dysfunction at baseline (VFT and RAVLT tests). Older age, low-level education, presence of comorbidities and colorectal as primary tumor were associated with lower scores in VFT assessment (all p<0.05). Regarding the RAVLT values, lower values were observed in older patients and in patients with comorbidities.

Moreover, a statistical association was found between marital status and executive function and attention (p=0.01) and also between sex and memory function (p<0.05).

Nonetheless, variables such as performance status, alcohol consumption and smoking status were not found to be related to cognitive decline.

Additionally, anxiety and depression status were analyzed at baseline (HADS) and 16.1% of patients presented anxiety, 25.8% borderline condition and 1.61% depression symptoms and 16.1% borderline condition. Non-association with cognitive damage was found.

Quality of life (FACT) levels were not statistically related to cognitive impairment in our data.

Outcomes of neurocognitive tests at the three assessments time points
Figure 2 represents the median and interquartile range for each test in the three time points in the overall population and also in colorectal and breast cancer subgroups (the results are summarized in more detail in Table S4).

From the 62 patients evaluated in the first assessment, a total of 55 were assessed at the second time point. Out of these 7 losses, four were due to residual symptoms derived from chemotherapy and the patients were not able to undergo neurological assessment in optimal conditions. The others three patients refused to carried out the study. In the last evaluation, 45 patients were assessed because seven presented tumor disease progression at that time and three refused to continue.

In the overall population, verbal and visual memory and executive functions are the most affected domains in the second assessment (M1). However, they are only impacted slightly (median score 11 vs. 9 in Letter-Number sequencing). No significant differences were found between the results of the first and second assessments. It should be noted that in the TMT B test, 22.2% of patients recorded at least a 20% decline in their score at second assessment. Statistically significant changes were found in VTF, number sequencing, block design and visual tests during the evolution in the three assessments (Fig. 2). On the other hand, the outcomes of Stroop, Digit span and RAVLT tests did not experience changes throughout the three evaluations.

Regarding the type of tumor, at M1, there is a subtle trend of worse outcomes in the neuropsychological tests among the colorectal cancer cohort, especially in visual memory and attention, albeit non statistically significant (visual test median scores 70 vs. 45, letter-Number sequencing 11 vs. 10.5 and number sequencing median scores 10.5 vs 10 between pre and post chemotherapy respectively).

**Cognitive impairment in the three assessment periods**

Figure 3A shows the evolution of cognitive impairment in the whole test battery except TMT. In the pre-chemotherapy setting, 9 out of 62 evaluable patients (14.5%) had cognitive dysfunction. The criterion of z scores of $\leq -1.5$ for more than one test was met by five of these patients, two met the criterion of z scores of $\leq -2.0$ for one test, and two met both criteria. On average, these patients showed decrease in 2.3 tests, whereas those without cognitive dysfunction showed it in 0.17 tests (Mann–Whitney p<0.001).

In the second assessment, at the end of chemotherapy, 8 out of 55 patients at that moment (14.5 %) experienced cognitive impairment. Two of these patients met the criterion of z scores of $\leq -1.5$ for more than one test, five met the criterion of z scores of $\leq -2.0$ for one test, and one met both criteria. These patients had impairment in 2 tests and patients without cognitive damage failed in an average of 0.23 tests (Mann–Whitney p<0.001).

Finally, in the late follow-up (n=45), 9 of 45 patients (20%) had shown cognitive dysfunction. Three of them met the criterion of z scores of $\leq -1.5$ for more than one test, four met the criterion of z scores of $\leq -2.0$ for just one test, and two met both criteria. These patients had, as an average, impairment in 2.3 tests vs. 0.11 in patients without cognitive impairment (Mann–Whitney p<0.001).
Cognitive function dynamic evolution

Finally, we studied the intra-patient evolution from baseline (M0) according to the battery of 9 tests. A total of 61.9% of patients presented a decline in scores in 4 or more tests from baseline to post chemotherapy evaluation (M1). This percentage decreased to 24.4% in the later follow up evaluation, showing intra-patient recovery after chemotherapy (M2) (Figure 3B). At M2, 33.3% patients presented a better score in 6-7 tests in comparison with the pre-chemotherapy assessment.

If we analyze intra-subject evolution for each test separately, it should be noted that from M0 to M1 there were 67% patients with a lower score in RAVLT, 53% of patients had a worse VFT score and 55% of them achieved worse outcomes in the Letter-Number sequencing test. Moreover, 20.4% and 22.2% of patients obtained significantly worse results in TMTA and TMTB test respectively. Otherwise, from M1 to M2 there was a recovery in the outcomes of VFT, number sequencing and block design tests in 69%, 60% and 71% of the patients respectively. The cognitive area with the greatest decline is visual and verbal memory.

Discussion

Chemotherapy has been identified as one of the main causes of cognitive impairment in patients with cancer.

This prospective longitudinal study includes both early breast cancer and colorectal cancer patients with cognitive function evaluation in three different time points, including an assessment prior to chemotherapy initiation, within the first month after completing the treatment and between 24 and 30 weeks after the end of chemotherapy. To our knowledge this is the first study that simultaneously includes different tumor types, trying to elucidate the real neurotoxicity of chemotherapy regardless of the primary tumor or antineoplastic drugs used.

We included a comprehensive battery comprised of 11 tests evaluating different skills, allowing a more complete analysis compared to other longitudinal studies (28, 29), and additionally used recommended objective tests (5). Therefore, our study analyses cognitive assessment using validated questionaries that avoids self-reported cognitive decline, which magnify subtle differences, with worse correlation in terms of neuroimaging and higher sensitivity to emotional status (8, 30, 31).

Our study sheds light not only on the effect of chemotherapy on cognitive function, but also on its own dynamic evolution over time in patients receiving chemotherapy due to its longitudinal and prospective design.

Our data suggests that 61.9% of patients experienced a substantial decline in their cognitive function after chemotherapy. This is consistent with other longitudinal studies in woman with breast cancer that have reported rates from 45.2–65% (8, 32, 33) and also in colorectal cancer patients with rates between 46% and 56% (9, 28).
Of note, in our study 37.5% of patients experienced a recovery in cognitive abilities at the late follow-up assessment, which means that most of the patients with cognitive decline after chemotherapy are able to overcome it over time and CRCI could be transient and reversible. Nevertheless, 24.4% of the patients persist with worse cognitive function compared to baseline, at least in the six month follow up. Other studies suggest CRCI could persist 1 year after chemotherapy (33) and even 20 years after (6), although there are studies with controversial results (34).

Regarding the most affected cognitive dominions during the oncological process, our study agrees with previous ones in that verbal and visual memory are the most affected areas and, to a lesser extent, executive function(9, 28, 32).

Previous studies have identified age and years in education as a reliable predictor of performance in tasks (35). We confirmed these data and also added the presence of comorbidities, type of primary tumor (colorectal), sex and smoking status as potential variables associated with lower scores at baseline. Otherwise, anxiety, depression and QoL did not seem to be associated with CRCI in our cohort, whereas in others publications with patient complaint reports, these factors have been related to cognitive dysfunction (31, 36). Given the proportion of patients who are going to benefit from chemotherapy administration and are going to survive, the medical community should continue trying to identify risk factors for developing cognitive impairment as long-term toxicity.

Additionally, it is noteworthy that our study suggests that compared to the breast cancer cohort, the colorectal cancer subgroup has a trend of subtly worse outcomes from baseline to post chemotherapy assessments. A potential explanation could be the different drugs used in adjuvant colon therapy or patient characteristics (patients are likely to be older and with more comorbidities), no comparisons are accurate because other studies have not included different tumors. Further research with more patients should be attempted to confirm this observation.

Strengths of this study include its longitudinal and prospective design, our application of most of the recommended neuropsychological tests and interestingly, we have also analyzed two different cohorts, colorectal and breast cancer, being able to elucidated the different evolution of the cognitive function among them. On the other hand, our study has some limitations including the small sample size with a rate of attrition of 11.3% and 27.4% at moment M1 and M2 respectively, similar to other studies (37). Second, the heterogeneity of patients may complicate the interpretation of the results. Third, our study did not include healthy controls, despite this, the intra-subject comparison allows better understanding of the real changes in the individual evolution of cognitive function. And finally, the potential significant practice effect could impact on the results (38, 39). However, statistically significant differences have been confirmed even with the possibility of this practice effect. This should also be taken into account as a possible explanation of the fact that rates of development of cognitive impairment in our cohort were lower than previously reported (28).

In conclusion, cognitive function experiences changes during chemotherapy treatment, especially verbal and visual memory areas, and may be subtly but transiently affected during treatment, with most patients
recovering their cognitive function over time. Our study provides a new approach to examine the CRCI according to international recommendations in order to better understand the behavior of cognitive function evolution in patients undergone chemotherapy. CRCI remains a complex symptom that many patients could develop in the future. Further investigations are needed to prevent and treat CRCI among cancer survivors, and efforts to accurately define the features of CRCI should be performed in order to manage it properly. CRCI could impact not only on patients’ quality of life but also on their social and mental wellbeing, becoming an obstacle for reincorporation into work or for their social network after the oncological process.

Declarations

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Conflicts of interest/Competing interests:
*A.C. reports advisory role and/or travel compensation: Bristol-Myers Squibb Recipient, F. Hoffmann La Roche AG, Pfizer, Boehringer Ingelheim, MSD Oncology, Kyowa Kirin, Celgene, Leo Pharma, Medscape, Kern Pharma.

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Code availability: Code not available. Specific data will be available on request from the corresponding author.

Authors' contributions:
Conception and design: A.C., P.I. and R.A.

Provision of study materials or patients: A.C., P.I., J.A., A.Y., L.M., D.I. and R.A.

Collection and assembly of data: A.C., P.I., L.O., P.G., L.B., S.D., C.A., A.M., J.A., A.Y., L.M., D.I. and R.A.

Data analysis and interpretation: A.C., P.I., G.V. and R.A.

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**Ethics approval:** The project was designed according to the ethical principles of the Declaration of Helsinki, and, the approval of the regional ethics committee (CEICA record nº CP04/2016) was obtained.

**Consent to participate:** All participants provided written informed consent previously approved by the of the regional ethics committee.

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Tables

Table 1
Neurophysiological, quality of life and mental health tests categorized by studied domain.

| Area                        | Test                                                                 |
|-----------------------------|----------------------------------------------------------------------|
| Verbal and visual memory    | Rey Auditory Verbal Learning Test (RAVLT)                           |
|                             | Digit Span and Spatial Span from Wechsler Memory Scale (WMS-III)    |
|                             | PIEN (subtest of Barcelona test)                                    |
|                             | Letter-Number sequencing (WAIS III)                                 |
| Executive function          | Verbal fluency test (semantic and phonetic)                         |
|                             | Stroop                                                               |
|                             | Trail Making Test B                                                 |
|                             | Letter-Number sequencing (WAIS III)                                 |
| Attention and psychomotor function | Trail Making Test A                                            |
|                             | Digit Span and Spatial Span from Wechsler Memory Scale (WMS-III)    |
|                             | Number sequencing                                                   |
| Visuoconstructive function  | Block design (WAIS III)                                             |
| Anxiety and depression      | Hospital Anxiety and Depression Scale (HADS)                       |
| Quality of life (QoL)       | Functional Assessment of Cancer Therapy (FACT Breast and FACT Colorectal) |

Figures
Figure 1

Associations between clinicodemographic features and FVT and RAVLT tests at baseline. VTF Verbal Fluency Test; RAVLT Rey Auditory Verbal Learning Test
Figure 2

Median and interquartile range in each neuropsychological test at the three assessment time points in colorectal, breast cancer patients and the overall population. * Statistically significant (*p< 0.05) CRC colorectal; VFT Verbal Fluency Test; RAVLT Rey Auditory Verbal Learning Test
Figure 3

Cognitive changes during the assessment periods. 3A Patients with cognitive dysfunction at each time point and their evolution over time. 3B Dynamic evolution of the percentage of the patients with decline in neuropsychological tests between different time points.

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