REVIEW

Why, After Chemotherapy, is it Necessary to Assess Memory Using Translational Testing?

Summer F. Acevedo
Department of Physiology, Pharmacology, and Toxicology, Psychology Program, Ponce School of Medicine and Health Sciences, Ponce, Puerto Rico. Corresponding author email: sacevedo@psm.edu

Abstract: As the number of cancer survivors rises, so does the importance of understanding what happens post-chemotherapy. The evidence is clear that chemotherapy affects not only cancer cells, but also healthy cells including neurons, leading to long-term cognitive dysfunction in a large portion of survivors. In order to understand the mechanism of action and in the hope of reducing the potential neurocognitive side effects of chemotherapy, pre-clinical testing should be used more effectively. However, the field is lacking translation from clinical studies to animal models. Spatial learning and memory paradigms based on the water maze, the most commonly used rodent model, are available for translational testing in humans and could overcome this weakness. There is an overwhelming need in the field to understand whether the water maze is an adequate model for post-chemotherapy impairments or whether other paradigms should be used. This is of great importance for the understanding of the mechanisms, side effects of new drugs, appropriate pharmacotherapy, and confounding factors related to chemotherapy treatment regiments. This review is very important to both basic scientists and clinicians determining how translational paradigms are critical to future cancer research, as well as what type of paradigms are appropriate in our technically advancing society.

Keywords: water maze, cancer, memory, spatial, translation

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What Factors Affect Memory After Chemotherapy?

The prevalence of cancer has risen to epidemic proportions. Chemotherapy, the main treatment for cancer, is a disease treatment that makes use of chemical toxins that affect more than just cancer cells, leading to various symptoms that includes nausea, vomiting, fatigue, infection, and neuropathy, thus adversely impacting the treated individual’s quality of life. Regardless of cancer type, when chemotherapy survivors are asked how their treatments affected their mental processes, the majority report that their powers of recall are diminished and, in addition, they often complain of memory loss. Unfortunately, unlike children, adults are not examined for long-term cognitive effects, which may result from the chemotherapeutic agents. Many are not even told that memory loss or cognitive decline is a side effect of treatment.

Regardless of the type of cancer, chemotherapy and surgery are the two main methods of treatment. Adjuvant chemotherapy is generally necessary to battle breast cancer with the administration of the chemotherapeutic agent(s) either orally or intravenously. This type of treatment involves drugs that move through the bloodstream, destroying malignant cells in their different phases of growth. However, chemotherapy drugs do not only attack cancer cells but also cross the blood brain barrier and cause damage in several areas of the brain. This effect is variously known as chemo-brain and chemo-fog; both expressions are used to describe the cognitive decline some patients experience post-chemotherapy. The majority of studies that exist have been done with breast cancer patients because of their high survival rate, as well as the high rates of younger and middle-aged women who, after having undergone chemotherapy, complain of cognitive decline.

The chemicals used in chemotherapy induce negative effects on neurons, progenitor cells, and neurotransmitters involved in cognitive processing. Methotrexate and 5-Flourouracil (5-FU), the two most common chemotherapy drugs used to treat breast, colorectal, head, and neck cancers, have been examined in pre-clinical models because of their neurological effects. In rodent models, systemic 5-FU has been shown to lead to delayed damage of the white-matter tracts, causing damage to the central nervous system. Examinations of the hippocampus from 7 days to up to 1 month after single intravenous injections of methotrexate showed there to be reduced hippocampal cell proliferation. One particular regimen, Cyclophosphamide, Methotrexate, and 5-FU (CMF), has also been shown to lead to decreased hippocampus cell proliferation and altered chromatin remodeling in the hippocampus. In addition, carmustine (BCNU), cisplatin, and cytosine arabinoside (cytarabine) injections in mice lead to increased cell death and division in the sub-ventricular zone, dentate gyrus of the hippocampus, and corpus callosum. Injections of cisplatin, cyclophosphamide, thiotepa, or ifosfamide in young rats led to widespread cortical and thalamic lesions. The studies to which we have so far referred agree that chemotherapy drugs are neurotoxic, but how does that translate to humans and how can we assess damage in order to reduce the effects?

Imaging

Post-chemotherapy mental deficits are specific to a given patient and cannot be generalized. Small differences may not be detectable by standardized tests, or indeed the patient may simply be able to compensate for any difference(s). As a result, recent studies have utilized brain imaging as a potential measure of post-chemotherapy neurological damage. Studies in breast cancer survivors have found smaller grey and white matter 1 year after chemotherapy in several areas, including the parahippocampal gyrus and prefrontal regions, both of which are linked to attention, concentration, and visual memory. Drugs such as ifosfamide have side effects that include hallucinations, dizziness, confusion, and hemiparesis and have led to comas. Leukoencephalopathy, a disease that destroys the brain’s white matter, has also been reported as a neurological complication associated with such chemotherapy drugs as 5-FU, cisplatin, levamisole, methotrexate, and pirarubicin. Neuroimaging has led to early detection of leukoencephalopathy, and with subsequent steroid treatment, the effects of leukoencephalopathy are reversible, regardless of the age of the sufferer. In support of the idea of tracking, it can be beneficial to use neuroimaging techniques on patients who show any signs of cognitive decline. However, a review of the literature indicates that the histological lesions in human brains that result from these types of neurological conditions are different than those found in animal models, which may limit...
the usefulness of such imaging for translation to pre-clinical models.

**Standardize Neurocognitive Testing**

There are more than 30 reviews that list all of the different tests used and domains tested in the examination of neurocognitive deficits after chemotherapy. There are more than 30 reviews that list all of the different tests used and domains tested in the examination of neurocognitive deficits after chemotherapy.5,11,26–36 Studies vary significantly in terms of the tests used, sample sizes, and whether or not pre-chemotherapy testing was done. In addition, there is a huge variety of confounding factors related to neurocognitive assessments.37 There are many confounding biological factors to consider in these studies, including types of controls, age, gender, stress levels, menopausal status, and whether or not a given sample group member is undergoing hormone therapy. The list goes on and on.

When assessing post-chemotherapy cognitive status in older individuals, age-associated cognitive decline and the assortment of sensory and memory issues generally linked to aging must also be taken into account.37 With advances in technology, we are beginning to observe more individuals under 50 years of age being diagnosed with cancer. These individuals still have many years of work ahead of them. Memory is essential to their ability to function properly. These individuals are also more likely to be subjected to more intense treatment regimens to prevent the recurrence of their cancer. This may explain why younger individuals appear to be more cognitively affected by chemotherapy than their older counterparts.2,38 Even when slight, the cognitive effects of chemotherapy can negatively impact work performance and the ability to care for children.29,39,40 In addition, some individuals become so impaired they are no longer able to maintain their jobs or careers, making the stress of caring for their families that much harder. Very few studies have examined younger patients (those under 40) and the impact of chemotherapy in that group. We need to keep in mind that younger patients are greater users of technology and that the types of assessments for memory that involve computer-based programs can and should therefore be considered.

Recommendations have been made by the International Cognition and Cancer Task Force (ICCTF) to include measures of learning and memory, processing speed, and executive function (Hopkins Verbal Learning Test-Revised [HVLT-R], Trail-Making Test [TMT], Controlled Oral Word Association [COWA], and the Multilingual Aphasia Examination) as standard batteries in the clinical testing of post-chemotherapy patients. The ICCTF recommends that future clinical studies include pre-chemotherapy testing, consider sample size, and use controls appropriately. The ICCTF further recommends that additional standardized methods of analysis need to be developed for use in such studies. Even if there is more standardization, what are these tests going to tell us and how can we improve treatments? Are the standard pen/pencil or puzzle-like neurocognitive assessments to measure intelligence, executive function, visual memory, motor coordination, and psychomotor speed really valid to help us understand the mechanism of impairments? All of these tests have one thing in common:—they do not translate to pre-clinical models (Fig. 1). The issue is how sensitive are the measures and how that information can be translated to neuronal functioning and an understanding of the mechanism of action in pre-clinical models.

**Why is it Important to Translate Animal Models to Clinical Testing?**

An important issue to consider is that not all individuals will display similar cognitive impairments even if undergoing the same regimen. Every individual is unique and his or her response to drugs and the type of cancer they have will alter the treatment received. It should also be noted that chemotherapy drugs are administrated as part of a complete regimen, with other medications included in order to reduce side effects; how these medications interact and effect cognition makes the results of clinical testing almost impossible to interpret. In terms of neurocognitive testing itself, there are many studies that examine the domains and the types of tests used for those in the post-chemotherapy phase. In the more than 50 studies that have been conducted to examine the long-term effects of chemotherapy, only a handful have included visual-spatial tasks; these types of tasks are paradigms that can be used to translate between clinical and pre-clinical models. Those tests that have been used have included the Block Design test, which is a subtest of Wechsler’s Adult Intelligence Scale-III that uses colored blocks to represent a design (Fig. 1), and the Rey-Osterrieth Complex Figure Test (RCFT),...
a memory test that is used to assess visuospatial
construction or Visual Reproduction, a subtest of
the Wechsler’s Memory Scale—Revised (WMS-R)
(Table 1).46–50 The results of these studies do not agree
on whether chemotherapy impacts long-term visual-
spatial memory, but the tasks used vary significantly
and are, it should be noted again, not translatable to
pre-clinical models (Table 1).

The Morris water maze (MWM)51 is the most
commonly used and recognized spatial learning and
memory test used for the pre-clinical assessment of
drug use and various confounding factors such as
genetics, age, and gender, assessing these both in
terms of acute and long-term learning and memory
effects (Fig. 2). This rodent based test has been used
for the understanding of the mechanism of neuro-
physiological/neuro-anatomical changes and can be
used to assess learning and memory in a way that is
translatable to humans. The drugs that are part of
the CMF regimen have been studied extensively in ani-
mals in terms of their acute and long-term cognitive

effects using the MWM task. Examination at 7 days
and 1 month after a single intravenous injection of
methotrexate induced impairments in a MWM probe
trial and delayed memory performance and novel
object recognition.13,14 In mice injected intraperito-
neally (i.p.) weekly with methotrexate, impairments
were apparent in initial hidden spatial memory in a
MWM.52 There have also been studies in pre-clinical
models that have not shown there to be long-term
cognitive impairments in animals that perform the
MWM after repeated treatments with CMF.53,54 Of
all these experiments, time between exposure and
testing, number of injections, and type of test varied
significantly. More consistency between studies is
needed to definitively determine whether this para-
digm mimics the cognitive effects seen in humans.

Additional medications are administered for
women with estrogen positive cancers, including taxol
(tamoxifen), which is an estrogen receptor modulator
(SERM). Compared to women on chemotherapy
alone, those women who received chemotherapy and
tamoxifen scored lower in visual memory and verbal
working memory (Table 1).47,49,55 A follow-up study of
women who continued to take taxomifen for at least
5 years after chemotherapy treatment as a prevention
measure also found that they fared negatively
when compared to non-tamoxifen users, with more
complaints of memory problems and reduced scores
on narrative writing task.56 In rodent models, repeated
administration of tamoxifen or combinations of
methotrexate and 5-FU injections both produced
deficits in acquisition and retention in an operant
learning paradigm.57 Although the tests are not
comparable, they indicate that secondary treatments
are a potential confounding factor to consider when
assessing post-chemotherapy neurocognitive side
effects. Evidence supports that secondary drugs
### Table 1. Chemotherapy and visual spatial impairments in humans.

| Ref | Groups | Cancer Type | n  | Sex | Testing Age | Treatment       | Test used       | Effect of Chemotherapy |
|-----|--------|-------------|----|-----|-------------|-----------------|-----------------|------------------------|
| 47  | Chemotherapy | BC Stage I-IV | 19 | F   | 42.6 ± 5.4  | Pre/Post (1 week, 1 year) | RCFT – Immediate Recall | No effect |
|     | Chemotherapy + Tamoxifen | BC Stage I-IV | 19 | F   | 40.1 ± 6.5  | Pre/Post (1 week, 1 year) | RCFT—Delay Recall | No effect |
|     | Surgery only | BC Stage I-II |    |     | 44.5 ± 4.1  | Surgery only     |                 | No effect |
| 48  | Chemotherapy | BC Stage I-IV Lymphoma | 36 | F/M | 48.6 ± 8.0  | CEF (Pre/Post)   | RCFT—Copy       | No effect |
|     | Cardiac     |             | 14 | F/M | 40.4 ± 9.1  | RCFT—Immediate Recall |                 | No effect |
|     | Healthy     |             | 17 | F/M | 39.3 ± 11.7 | RCFT—Delay Recall |                 | No effect |
| 49  | Chemotherapy | BC Stage I-II | 18 | F   | 46.8 ± 4.0* | CMF             | Visual Reproduction I (WMS-R) | Effect |
|     | Chemotherapy + Tamoxifen | BC Stage I-II | 18 | F   |             | ACT             | RCFT—Copy Trail | Effect |
|     | Surgery only | BC Stage I-II | 17 | F   | 48.3 ± 6.3  | Block Design (WAIS-III) |                 | Effect |
| 50  | Chemotherapy | BC Stage I-II | 18 | F   | 47.1 ± 6.5* | CMF (3 years)    | RCFT—Copy       | No effect |
|     | Chemotherapy + Tamoxifen | BC Stage I-II | 18 | F   |             | CMF (3 years)    | RCFT—Immediate Recall | Effect |
|     | Surgery only | BC Stage I-II | 34 | F   | 46.1 ± 5.2  | Visual Reproduction (WMS-R) |                 | Effect |
| 65  | Chemotherapy | BC Stage I-IV | 22 | F   | 46.7 ± 3.8  | Various (Post only) | Memory Island – Immediate Recall | Effect |
|     | Healthy     |             | 16 | F   | 52.5 ± 2.0  |                 | Memory Island – Delay Recall | Block Design (WAIS-III) | No effect |

**Note:** Age was reported for combined Chemotherapy and Chemotherapy + Tamoxifen groups.

**Abbreviations:** RCFT, Rey-Osterrieth Complex Figure Test; CMF, cyclophosphamide, methotrexate, and 5-FU; ACT, adriamycin, cytoxan and taxol; CEF, cyclophosphamide, epirubicin and 5-FU; Pre/Post, Chemotherapy; BC, Breast Cancer; WMS-R, Wechsler’s Memory Scale – Revised; WAIS-III, Wechsler abbreviated scale of intelligence.
such as raloxifene, letrozole or exemestane (SERM/ aromatase inhibitors) may be better alternatives to the more commonly used tamoxifen, as they appear to have fewer or no confounding side-effects on overall cognitive health.\textsuperscript{55,58–62} Although these drugs are newer to the market, they tend to be more expensive and as only a few studies are available, both doctors and patients have to consider options and weigh risks.

Today’s technology is advancing and so are the available methods of assessing learning and memory impairments. Using human versions of visual-spatial memory tasks such as the “Memory Island” (MI) program is a useful way of helping to transition from pre-clinical models to a clinical setting (Fig. 2). MI is a virtual reality program designed to mimic the MWM four-quadrant coordinate system. In MI, individuals find both visible (marked) and hidden targets on a virtual island designed by Dr. Jacob Raber (Oregon Health Science University) and Dean Inman (Oregon Research Institute) (Fig. 2).\textsuperscript{63} Performance measures are the same as in MWM, wherein distance, latency, velocity, and distance from the target can be assessed. MI examines motor coordination, working memory, picture recognition, visual-spatial memory, and verbal/non-verbal ability.\textsuperscript{63–66} MI can also be an appropriate measure of visual-spatial learning and memory suitable for use in multiple (non-English speaking) cultures, as it is considered a non-verbal test.\textsuperscript{66} MI adequately assesses depth perception, visual-spatial attention, figure-ground discrimination, spatial perception, and orientation.\textsuperscript{63–66} Furthermore, these types of paradigms can be utilized as quantitative and qualitative measures in research projects or for clinical screening following traumatic brain injury, as well as in the assessment of Alzheimer’s disease or other neurodegenerative conditions. Additionally, there are other tests that result in data that are easily translatable to clinical settings; these include Novel Image/Novel Location tasks, which examine spatial picture location recognition and are used to model novel object recognition in pre-clinical models.\textsuperscript{63,65,66} There have also been significant advances in touch screen technology to translate rhesus monkey working memory tasks into clinical assessments.\textsuperscript{67,68}

Determining the long-term cognitive deficits that result from chemotherapy remains an urgent need and one that can be fulfilled through the use of translational paradigms.

In breast cancer survivors who were a minimum of 1 year post-chemotherapy (mixed regimens), a study found reduced performance in MI performance measures in terms of both immediate and delayed spatial memory when compared to health controls (Table 1).\textsuperscript{66} The breast cancer survivors were able to learn the tasks to a similar degree as the controls, but took longer to find the targets once the visible cues were gone (hidden trials).\textsuperscript{69} After 15 minutes in the delayed memory trial, only 50% of the breast cancer survivors were able to find the target compared to the 82% of healthy controls that were able to do so (Table 1).\textsuperscript{66} The results are similar to those found in the rodent model of long-term chemotherapy exposure.\textsuperscript{14,15}

The study also found that particular coping strategies were associated with MI performance. Those that use emotional coping displayed reductions in learning and immediate MI performance when compared to those who use more problem-focused coping.\textsuperscript{66} Those that used problem-focused coping also performed better in delayed spatial memory performance, had higher general intelligence scores, and showed an increased ability to perform psychomotor speed tasks. Understanding the link between coping and cognition can help in the development of behavioral therapies to help patients resume normal functioning. Although this was only a pilot study and did not account for pre-chemotherapy differences, it does help to validate the use of MWM in pre-clinical testing for the assessment of the cognitive effects of chemotherapy drugs. Future longitudinal studies will include more subjects to assess different chemotherapy regimen effects as well as genetic, age-related, and other potential confounders.

**Conclusion**

In the era of technology, scientists and clinicians alike need to adapt to the tools available. The overall goal has always been translation of bench to bedside, but we have to know if the bench is truly examining what is actual taking place as a result of a disease and/or treatment for that disease. Although, cancers such as breast cancer do not affect the brain per se, there is clear evidence that the treatments do have an effect on a significant proportion of patients. We have to consider a patient’s overall health, well-being, and ability to function after treatment, which includes reintegration into daily function and/or work environments. We need to make it a
priority to reduce the side effects of the drugs used and to optimize the use of appropriate animal models. MWM is the most widely used behavioral paradigm in rodents and is used for the examination of all manner of treatments and diseases models, but is it really the best model for every condition that affects the brain? Does it truly examine what happens in humans? These questions are critical for the future of model system research. Most chemotherapy drugs have never been tested with respect to long-term cognitive effect in rodents and need to be in order to help identify those with minimal side-effects. MWM is the old standby with respect to examining long-term cognitive side effects post-pharmacotherapeutic intervention; however there are other translational paradigms such object recognition and fear conditioning rodent-based paradigms that have recently been adapted for clinical studies. Researchers and clinicians alike need to determine how and what paradigms should be used in both pre-clinical and clinical settings.

There is also a serious lack of communication between clinicians, neuropsychologists, and neuroscience researchers. When examining cancer patients post-treatment, clinicians take advantage of neuropsychologists’ advice to design testing batteries, and basic scientists for pharmacological efficacy; however, they do not take advantage of what a behavioral neuroscience animal model researcher could bring to the table. I propose that when batteries are constructed in clinical studies for the purpose of examining neurocognitive status (post-pharmacotherapeutic intervention), a behavioral neuroscience animal model researcher needs to be involved in the development, in order to help insure that translational testing is used, thus aiding in the study of the mechanism. Translational testing should be the norm, not an afterthought. Behavioral neuroscience researchers understand that the point of the treatment is to cure the disease first and foremost, but they also understand how detrimental the neurocognitive side effects of the treatments can be on a patient’s functioning post-treatment. Only by working together can we help make the patient diseases free while also increasing the probability of them regaining normal functioning.

We can also use technology in memory based rehabilitation programs. First of all, as standard of care all patients undergoing chemotherapy should have neuropsychological assessments completed before treatment is initiated; therefore, a neuropsychologist can assess pre-morbid functioning. Patients that display reduced cognitive functioning post-treatment have several options of rehabilitation measures, depending on the type of impairment. For example, there are computer memory exercise programs, memory practice drills (repeating word list), spaced retrieval interventions (SR) and applied neurocognitive interventions (Mnemonic training, Prospectve Memory Process Training (PROMPT), errorless training, Assisted Mirror Reading) available for to help patients in restoration (rebuilding lost abilities), reorganization (substituting current abilities for those lost). There are also tools to help the patient during treatment work for both acute and long-term disorienting side-effects, including memory notebooks, electronic organizers, and environmental modifications. Most critical of all is keeping the patient brain active and helping patients maintain normal day to day activities.

**Future Prospective**

Considering the diversity of treatments and symptoms, the wonder drug that can cure all cancers and has no side effects will not be found. What we can do is reduce the impact and intensity of cognitive side-effects by taking into account an individual’s genetics. Genetic studies involving genes such as Apolipoprotein E (ApoE), which has three common alleles (ApoE2, ApoE3 and ApoE4), suggest ApoE4 carrier status as a potential genetic risk factor in the early-onset of breast cancer and neurocognitive impairments post-chemotherapy. ApoE4 carriers displayed several impairments, specifically in visual memory and spatial ability, providing at least primary evidence that ApoE genotype may be a confounding factor when assessing cognitive status. The clinical study is consistent with rodent models, where transgenic mice expressing human ApoE4 display behavioral abnormalities such as deficits in MWM performance, as well as significant alterations in the hippocampus and cortex. Several studies conducted in the last few years, have consistently found that the response to particular chemotherapies and hormone therapies appear to be ApoE genotype dependent. This strongly suggests that future studies must address the confounding factor of an individual’s genetics. The future of medicine will require tailoring a patient’s treatment based not only on the type of cancer and tumor profile, but also that individual’s genetics and how that will affect the potential side-effects of the treatments.
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Author(s) disclose no potential conflicts of interest.

Author Contributions
Conceived and designed the experiments: SFA. Analysed the data: SFA. Wrote the first draft of the manuscript: SFA. Contributed to the writing of the manuscript: SFA. Agree with manuscript results and conclusions: SFA. Jointly developed the structure and arguments for the paper: SFA. Made critical revisions and approved final version: SFA. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics
As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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Supplementary Data
A video abstract by the authors of this paper is available. video-abstract10293.mov