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Edited by Robert B. Raffa and Ronald J. Tallarida

Chemo Fog

Cancer Chemotherapy-Related Cognitive Impairment

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DEDICATION

To our families, with love and gratitude…

…and to the patients who speak up about chemo fog/chemo brain and the healthcare providers and researchers who listen to them.

PREFACE

Cancer patients have benefitted greatly from recent advances in the drugs, dose regimens, and combinations used to treat their primary tumor and for the treatment or prevention of spread of their disease. Due to the advances in chemotherapy and other aspects of prevention, early detection, and treatment modalities, an increasing percentage of patients are surviving the disease. For some types of cancer, the majority of patients live decades beyond their diagnosis. For this they are forever thankful and appreciative of the drugs that helped lead to this increased survival rate.

But no drug is devoid of adverse effects. This also applies to chemotherapeutic agents. The acute cytotoxic effects of these agents are well known—indeed are often required for their therapeutic benefit. The chronic adverse effects are varied and in some cases less well known. With the increase in survival rates, there has emerged a new awareness of these chronic adverse effects.

The adverse effects include pain, visual impairments, anxiety, and impairment of memory and cognition. Not every patient experiences all of these and some, the fortunate ones, experience none of these. But the general problem is real. The editors of this book are professors who are engaged in research on areas that compromise the total healing of body and mind in this patient population. One particular component of the need for survivor care is the memory problems and cognitive deficits experienced by some. The condition has been given a name—actually many names, such as chemo fog, chemo brain, and others. These names reflect the belief that the cause of the problem is the chemotherapy that they received as part of their treatment. In some cases the chemo fog/chemo brain is transient while in others it is of longer duration. Little is known about this problem and that fact peaked our interest and motivated this book. Therefore, this book is devoted to one aspect of survivor care: chemo fog/chemo brain. The current thinking can be summarized succinctly:

- It is not clear that it exists.
- If it exists, it is not clear what caused it (the chemotherapy, the disease, or some other factor, such as depression, the onset of menopause, etc.).
- If chemotherapy-induced, it is not clear which drug(s) or drug combination(s) are causative.
- No ‘prophylactic’ or ‘treatment’ is known.
- Most survivors adjust, but some have problems with their jobs or interpersonal relationships.

The material presented here provides background about the historical development of, and insight into, this condition. It also provides the 'state-of-the-art' of research (clinical and basic) and direction for future study. As such, the book should be of interest to students and the general reader as well as to patients and healthcare specialists. Toward this end, we have included chapters from a diverse set of authors who approach the subject from different perspectives. Each chapter was written in a way that it can be read independently of the others, but with a uniformity that allows smooth transition from one chapter to the next. It was our fundamental goal that this book provides the reader with an opportunity to quickly get 'up-to-speed' on this topic. More in-depth information is available from a variety of sources and so an extensive bibliography is provided.

Finally, we wish to point out that the preparation of this book represents a first step by the editors in launching the work of the Forget-Me-Not Foundation, whose mission is fostering improved care for cancer survivors.

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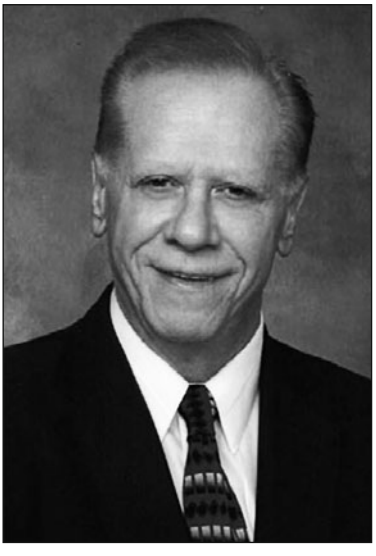

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Chapter 1

Short Introduction and History

Robert B. Raffa*

Abstract

If one does a MEDLINE® search using as keywords chemo fog or chemo brain or their hyphenated equivalents, fewer than 30 'hits' appear. The oldest dates back to 2003. This small number of hits in some way captures one aspect of the current state of the phenomenon (or phenomena). In contrast, if one does the search using 'cognitive × cancer × chemotherapy', hundreds more hits appear. This in some way captures another aspect of the phenomenon. It is both little-known and well-known. To go a step further, some data suggest that it is one of the most common adverse effects of chemotherapy, other data suggest that it does not exist. Even its name (or lack thereof) is still unsettled. Yet, patients consistently report it. This chapter introduces the reader to the fascinating and complex challenges—to patients, healthcare providers, basic scientists, employers, insurers and others—inherent in this topic and the current state of knowledge about it.

Introduction and History

One of the earliest references to cognitive effects of chemotherapy in cancer patients, at least in the English language literature, is that of Silberfarb et al in 1980 (summarized by Aluise et al in Chapter 19).[1] The authors reported "... cognitive impairment to be a common occurrence in the absence of affective disorders or other psychopathology. Chemotherapy was the major variable associated with cognitive impairment in these patients." This succinct statement fundamentally summarizes the state of knowledge of the field today as well as it did nearly 30 years ago. But the devil is in the details:

- 'Cognitive impairment': Compared to what (e.g., age-matched healthy controls, other chronic or serious disease patients, pretreatment)? What modalities of cognitive function?—all modalities to some extent or some to a greater extent (e.g., memory)? Is it debilitating? Does it resolve with time or does it get worse? Is there prophylaxis or treatment for it?
- 'A common occurrence': What percent of patients?—all patients in a certain subset (e.g., age, type of cancer, gender, etc.) or similar percent of all subsets? Is it more common in certain type(s) of caner (e.g., mostly brain cancer)?
- 'In the absence of affective disorders or other psychopathology': By today's standards with the advantage of more sensitive evaluative tools? What about depression known to accompany chronic medical conditions? What about other factors (e.g., onset of menopause, aging, etc.)?
- 'Chemotherapy': Which drug or drugs?—the ones in use today? Is it the drug(s) alone or when the drugs are administered with radiation? Is it particular regimens or combinations of drugs?

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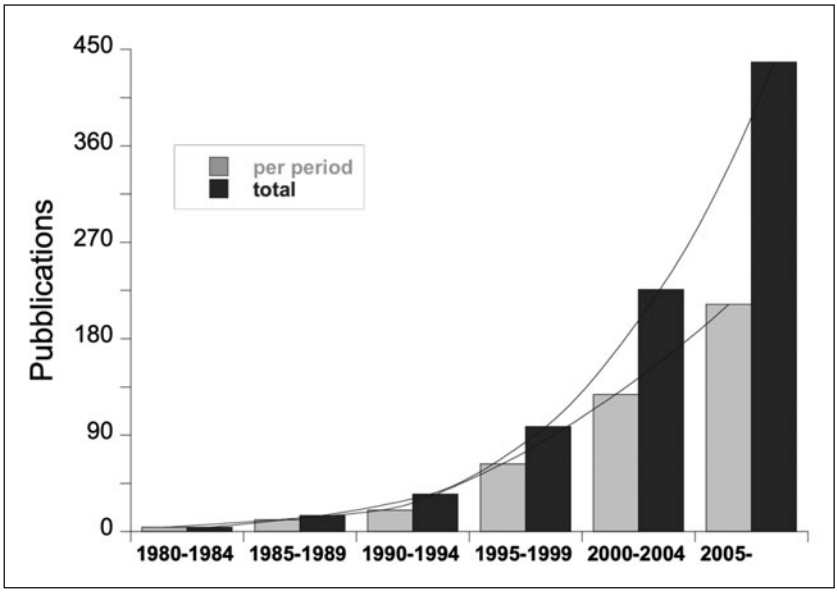

Figure 1. Trend in the number of publications on cognitive impairment and chemotherapeutic agents.

These questions are all relevant today and are all still the subject of investigation and even some debate and dispute. The original statement by Silberfarb et al in 1980[1] plus these questions, essentially summarize the state of the field of chemo fog, chemo brain, or whatever name, as it exists today. The statement plus the questions also essentially summarize the contents of the chapters of this book, each of which is devoted to one or more aspect of the overall field.

Since the publications by Silberfarb and colleagues, there has been an increasing interest in the (proposed) condition and an increasing number of publications on the topic, appearing at an increasing rate (Fig. 1) (see Appendix for a partial bibliography).

It was recognized early and is fairly well accepted, that treating young children with radiotherapy and to a lesser extent, chemotherapy (primarily methotrexate) causes CNS toxicity that manifests in a variety of ways, some not so subtle.[2-4] Cognitive impairment is one manifestation of these adverse effects. It certainly seems plausible, even obvious, that cranial radiation would cause cognitive impairment, but chemotherapy continued to be suspect.[5,6] The link continued to be investigated and documented and clinical practice evolved to limit cranial irradiation whenever possible.

A seminal paper was published in 1998 that reported cognitive impairment in patients undergoing adjuvant chemotherapy for breast cancer.[7] These patients did not have brain cancer and they did not have brain irradiation. So a connection between cognitive impairment and chemotherapy per se was solidified. An editorial that accompanied the paper made several important points:[8]

> "In this issue of the Journal, van Dam et al take an important first step in assessing the prevalence of cognitive dysfunction in women who received adjuvant treatment for highrisk breast cancer. Clinical reports of cognitive changes after high-dose adjuvant therapy for breast cancer prompted this systematic evaluation. The design of the study is important, for it is probably the first to examine comprehensively cognitive functioning in patients with breast cancer within the context of a randomized trial. A further strength is the inclusion of a Stage I breast cancer comparison control group that had not received any adjuvant treatment. The use of a disease-specific comparison group permits control for the impact of the diagnosis of cancer on psychologic

> distress and quality of life, both of which might affect cognitive functioning. Finally, the use of a battery of standardized neuropsychologic tests with healthy population normative reference data provides another important comparison. The key findings from the study include the following: (1) any adjuvant therapy increases the likelihood of women reporting cognitive problems in daily life in comparison with breast cancer patients who have not had adjuvant therapy; (2) emotional well-being, as determined by a standardized measure of QOL, does not differ in breast cancer survivors according to receipt of adjuvant chemotherapy; (3) there is a strong correlation between depression and anxiety and self-reported daily difficulties with concentration, memory and thinking; (4) breast cancer patients who have received adjuvant therapy are significantly more likely to be classified as cognitively impaired on standardized tests; and (5) logistic regression analysis demonstrates that the risk of cognitive impairment is substantially increased for patients who receive high-dose chemotherapy when compared with patients in the control group and when compared with the patients in the standard-dose chemotherapy group."

Several limitations of the study were noted, many of which apply (often unavoidably) to almost every study since:

> "... the small sample sizes of the treatment and control groups, the multiplicity of statistical comparisons, the cross-sectional design and the limited information about the potential mechanisms for the cognitive abnormalities. Furthermore, we are not told whether the measured differences in cognitive functioning in these survivors were associated with clinical disability or an inability to work."

The conclusion is clear:

> "Nevertheless, the study suggests a credible dose—effect relationship between adjuvant therapy and cognitive impairment".

These statements are as applicable today as they were then. Childhood cancer and cancer of all types continue to be major problems worldwide (Fig. 2). But with advances in prevention and treatment, more patients than ever are surviving. Survival times are now often measured in decades rather than months. So non life-threatening adverse effects attributable to the treatments are becoming more apparent and are more likely to receive attention.

Motivated by a passing comment made by a colleague (Michael R. Jacobs, Pharm.D., Temple University School of Pharmacy), we traced the development of the field of chemo fog/ chemo brain and the relevant questions, in a review published in 2006.[9] We started by stating the contemporary status:

> "A diminution in certain cognitive functions is reported in some patients during and after adjuvant cancer chemotherapy. The phenomenon has been observed not only in patients receiving chemotherapy for brain cancer, but also in patients receiving chemotherapy for cancers in peripheral locales, such as the breast. The cognitive diminution is said to affect an estimated one-third of such patients.[10] It has become commonly known as chemo fog or chemo brain.[10-13] However, several recent reports have challenged the methodology of studies purporting to document chemo fog/brain and, therefore, its very existence."

The importance of the topic remains as stated then:

> "There is a pressing need to address this issue, because some patients choose to discontinue chemotherapy when they learn of the purported negative consequences on cognitive function and others may unnecessarily be subject to such adverse effects if chemotherapy is not beneficial. If certain drugs are more responsible than others for cognitive impairment, then, in the short term, clinical choices can be made on the basis of relative adverse effects on cognitive function and, in the long term, this potential adverse effect could be incorporated into drug-discovery screens, yielding future drugs producing less of the problem."

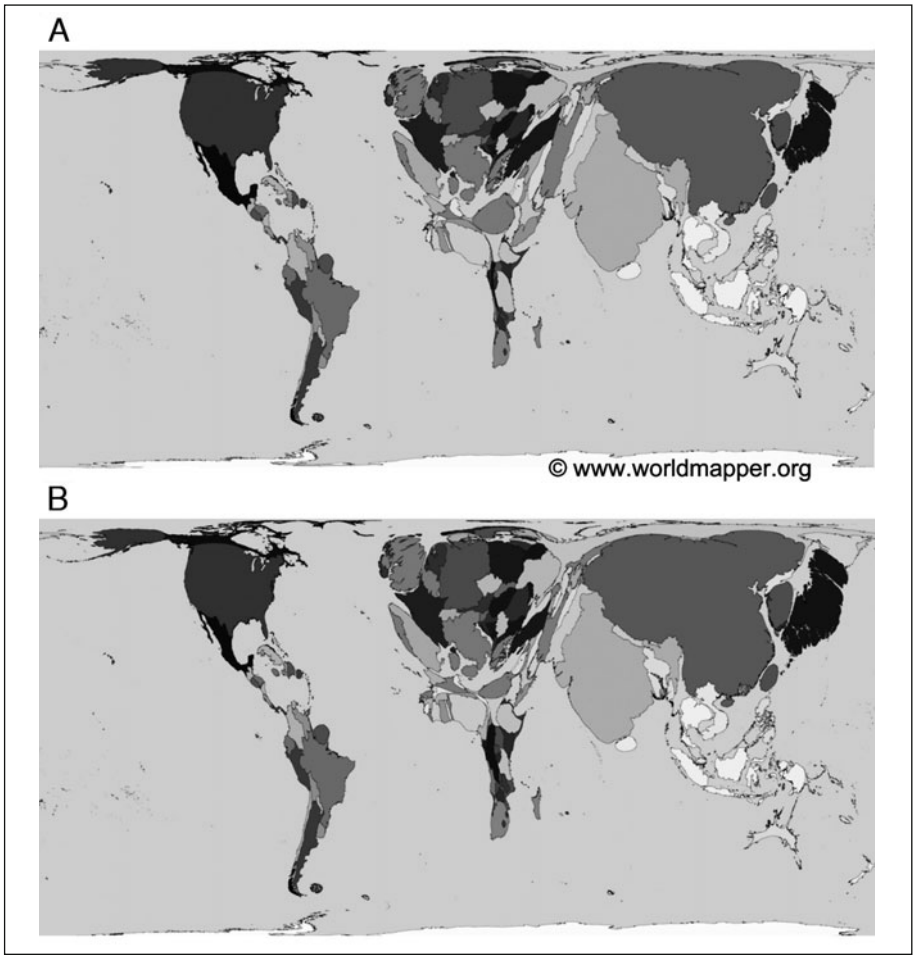

Figure 2. Leukemia (A) and total (B) cancer deaths. Territories are sized in proportion to the absolute number of people who died in one year. From WORLDMAPPER, with permission (http://www.worldmapper.org/display_extra.php?selected=434)

We raised a series of five questions then that can still serve as a basis for clinical and basic research today, because several of the questions remain unanswered despite many attempts to answer them:

1. Are there specific subjective or objective measures of the cognitive defect(s) that give rise to the terms chemo fog and chemo brain?
2. Is cognitive impairment associated with cancer itself, or other chronic illnesses, independent of chemotherapy?
3. Is it just chemotherapy, or do other treatment modalities (such as radiation or surgery) also produce chemo fog/'chemo brain'?
4. Do certain chemotherapeutic agents produce chemo fog/'chemo brain' more than do others?
5. Is there a rational mechanism for the production of such effects?

The state of the field up to the time of the review was summarized as follows, which still serves as a useful guide and introduction to the salient features of the field:[9]

> "The terms chemo fog and chemo brain are loosely used to describe self-reported or observed cognitive impairment that is said to occur in a subgroup of patients who receive adjuvant cancer chemotherapy to eradicate the growth of possibly fatal occult metastases (estimates range widely, from 4-75%)[7,14-20] and ongoing studies[13] even years after completion of therapy. Another term, 'chemotherapy-related cognitive impairment',[21] goes further, suggesting some causal link. The domains of cognition most often said to be impacted include verbal and visual memory, attention, concentration, language, motor skills, multitasking and ability to organize information.[11,13,22]
>
> There are several published studies that report occurrence of chemo fog/chemo brain in cancer patients who have undergone adjuvant chemotherapy.[1,7,14-20,23,24] In one study,[1] cognitive impairment (assessed by a battery of tests) was found to be a common occurrence in 50 consecutively admitted cancer patients. Another study[7] reported that two years (average) after cognitive functioning (using a battery of neuropsychological tests) in breast cancer patients was greatest (32%) in patients randomly assigned to receive high-dose chemotherapy (N = 34), compared to those who received standard-dose therapy (17%; N = 36), or to controls (early stage disease) who did not receive chemotherapy (9%; N = 34). A third study[15] reported a significantly higher risk of late (about two years after treatment) cognitive impairment (concentration and memory) in breast carcinoma patients treated with six courses of chemotherapy (28%; N = 39) than patients who received the same surgical and radiation therapy, but not chemotherapy (12%; N = 34). The cognitive impairment was unaffected by anxiety, depression, fatigue, or self-reported complaints of cognitive dysfunction. Another study[20] reported a higher incidence of moderate or severe cognitive impairment in women receiving adjuvant chemotherapy for breast cancer (16%; N = 110) than healthy age-matched controls (selected by the patients) (4%; N = 100). The greater cognitive impairment in breast cancer patients following chemotherapy (compared to healthy controls) has been reported to be independent of patient age or menopausal status.[17] Others[24] have reported persistent memory deficits (8-year follow-up) in children treated for acute lymphoblastic leukemia with chemotherapy (N = 17) compared to those who received cranial irradiation or to healthy controls. However, the children attained normal school levels. The remaining studies, likewise conducted with varying degrees of methodological rigor, reported similar findings. Thus, the existence of chemo fog/chemo brain appears to be well established, including studies that used objective outcome measures for documentation of impairment of specific domains of cognitive functioning. However, the methodology used in some of these studies has been criticized[12,25] and most did not permit an unequivocal establishment of a direct *causal* relationship with the chemotherapy.
>
> The occurrence of some form of cognitive impairment following chemotherapy for brain cancer would seem logical, even expected. However, chemo fog/chemo brain has been associated with a variety of peripheral cancers, including leukemia, prostate-, lymphoma-, testicular-, ovarian-, small cell lung- and breast-cancer.[13,26-28] Patient age is not a discriminating factor, since several studies have shown that children and elderly patients are susceptible.[26,28,29] Chemo fog/chemo brain has been most studied and most often associated with breast cancer.[13] The absence of sufficient information about its occurrence in men undergoing chemotherapy for breast cancer leaves open the question of a sex-specific phenomenon. There is a suggestion of a modest effect in young females, but not males, who had received central

> nervous system prophylactic chemotherapy for acute lymphocytic leukemia (2-7 yrs prior) (none had received whole brain radiation therapy),[30] but the numbers are too small to be definitive. In terms of time-course, chemo fog/chemo brain occurs in the short-term and may continue for years after treatment,[13,18,28] although some evidence suggests that it might be transient (recovery at 4 yrs post treatment).[16]"

We then addressed the individual questions. We first asked if there are specific subjective or objective measures of the cognitive defect(s) that give rise to the condition of chemo fog/chemo brain. We answered this question in the affirmative because the test batteries used in many of the studies, including CLOX (a clock-drawing test), EXIT25 (a 25-item bedside measure), High Sensitivity Cognitive Screen, FACT (Functional Assessment of Cancer Therapy)-Cog and CogState (a computer-based assessment battery), measure attention, concentration, verbal memory, visual memory, visual/spatial and speed of information processing. We noted, though, that it has been claimed that the batteries did not include sensitive tests of executive function and that they lacked insight into the 'real-world' impact of chemotherapy-induced cognitive decline.

We then asked if cognitive impairment had been previously linked to cancer or other chronic illness, independent of chemotherapy. We felt that it was agreed that there was sufficient objective evidence to conclude that cognitive impairment occurs in a subset of patients who receive chemotherapy for cancer. That is, "If a population of patients who have undergone chemotherapy for cancer are administered a standardized battery of tests, a detectable impairment in certain cognitive domains is noted".[1,7,14-20,23,24,31] What was and is, less clear is the role of the chemotherapy.[16] For example, it might be the biochemical aberrations of cancer itself or the impact of a serious illness that is the actual cause. It turns out that cognitive impairment had been reported in patients with other, nonmalignant chronic illnesses such as congestive heart failure (CHF),[32] Type 2 diabetes mellitus,[33] chronic obstructive pulmonary disorder (COPD)[34,35] and depression.[36] In fact, the cognitive impairments identified in these studies were overtly similar to those described for chemo fog/chemo brain. The depression that accompanies serious illness might play a role in the cognitive decline. A positive correlation between the number of depressive symptoms and cognitive impairment has been reported.[36] Thus, patients receiving cancer chemotherapy already have preexisting conditions, i.e., chronic illness and cancer, that predispose them to cognitive impairment. As discussed in other places in this book, unless a prechemotherapy baseline is established, or comparison is made to untreated cancer patients with the same malignancy, the identification of chemo fog/chemo brain in patients receiving chemotherapy—no matter how well controlled the study—does not establish causality with the chemotherapy. For example, in one study, 36% of the women in the study displayed cognitive impairment before initiation of systemic therapy. The authors concluded, as have others since, that cognitive impairment preexists in breast cancer patients prior to systemic chemotherapy and, thus, studies that do not control for this might overestimate the association of cognitive impairment with chemotherapy. Yet, we felt that there was sufficiency strong evidence from three studies to make a link. The first study[37] tested women newly diagnosed with breast cancer (a) presurgery, (b) at 2 weeks postsurgery and (c) 3 months postsurgery. The breast cancer group scored significantly lower on test measures related to capacity to direct attention than did the control group (age-matched cancer-free women) before treatment and showed only a gradual gain in capacity to direct attention over time. The second study[38] reviewed three prospective clinical research studies of patients undergoing adjuvant chemotherapy or hormonal therapy for breast cancer. The authors reported that approximately one-third of the patients exhibited impaired cognitive functioning on one or more of the tests, most often related to verbal memory (delayed recall) and verbal learning (long-term storage).[39] In previously published studies, the frequency of cognitive dysfunction ranged from 17% to 75%.[7,14,15,17,20] The third study was a retrospective comparison of women with operable breast carcinoma metastatic to the axillary lymph nodes who received adjuvant chemotherapy. Of the treated patients, 28% were found to have cognitive impairment compared to 12% of the control patients.[15] We concluded that adjuvant chemotherapy either has its own deleterious effect on cognitive function or it amplifies the effect of other factors, such as radiation or surgery.[40-42]

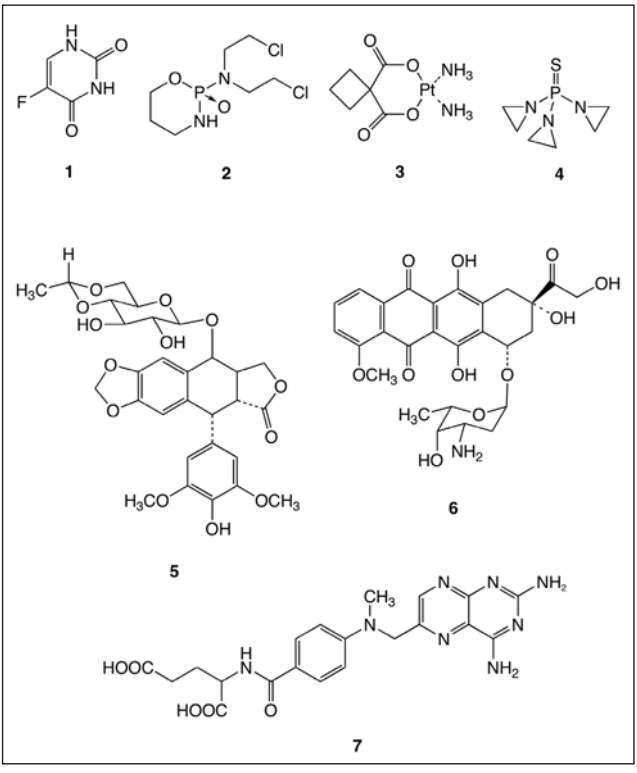

Figure 3. The chemical structures of some cancer chemotherapeutic agents. 1) 5-fluorouracil; 2) cyclophosphamide; 3) carboplatin; 4) thiotepa; 5) etoposide; 6) doxorubicin; 7) methotrexate.

We also asked if a particular drug (Fig. 3) or combination of drugs had been more closely associated with cognitive impairment.[43-45] Here, we were left with insufficient data to come to a conclusion, primarily due to the difficulty of finding controlled studies that used only one drug or one combination, without other medical therapy. This will almost certainly always remain the case. Ethical constraints preclude the necessary controls. This point will be addressed again later in the chapter.

We next asked if there is a rational mechanism by which a chemotherapeutic agent could lead to cognitive impairment. We reasoned that the first requirement for an agent to have this capacity is that it reaches the brain. In order to do so, it must be able to cross (or bypass) the blood-brain barrier. Although a number of anticancer drugs are lipophilic, many are substrates of the efflux pump P-glycoprotein. Their brain levels following systemic administration thus are low because of active transport out of the brain.[46] 5-Fluorouracil increases blood-brain barrier permeability,[47] but only transiently.[48] Actually, the relative inability of most agents to reach the CNS is a major problem in trying to treat brain metastases.[49] Cyclophosphamide and 5-fluorouracil and its metabolites penetrate normal brain, but to a lesser extent than does cyclophosphamide.[50] Methotrexate attains only minimal concentrations in normal brain. Some agents capable of crossing the blood-brain barrier have not been shown to cause toxicity.[51] Thus each agent and combination of agents needs to be evaluated. This topic, along with the proposed connections between drug-induced effects and cognitive impairment, is specifically covered in other chapters in this book.

Our final question was whether there were any proven preventative measures or treatments. We stated:

> "Since the cause of cognitive dysfunction in cancer patients is not known, prevention is problematic. 'Treatment' primarily consists of supportive measures (to alleviate symptoms or enhance cognition) or is experimental, based on proposed theories of causality. Practical measures such as convenient arrangement of the home or work environment, memorization exercises, the use of mnemonic devices, notes, avoidance of distractions, etc. are recommended.[13,52,53] Experimental pharmacologic measures include methylphenidate, modafinil, estrogen replacement, cytokine antagonists, anti-inflammatory agents, Alzheimer drugs, anti-anemia drugs and epoetin alpha (to increase red blood cell count and improve brain tissue oxygenation).[13,54] However, we are unaware of a study that has ... had something like the following four-arm design: Arm 1 = cancer patients given chemotherapy; Arm 2 = cancer patients not given chemotherapy; Arm 3 = cancer patients given chemotherapy plus 'treatment' and Arm 4 = cancer patients not given chemotherapy, but given 'treatment'. Without this type of study (which might not be ethically possible) positive results will remain circumstantial."

This topic is more comprehensively considered in other chapters of this book. The possible benefit of nonpharmacologic interventions, such as memory aids or exercises, or other interventions, should also be considered.

Overall, it appeared to us that:

> "... the best, perhaps the only, way to currently address the question of putative cognitive effects of chemotherapeutic agents, independently of the other complications associated with such therapy, is to directly test them in animal models. Such models can assess the effects of the drugs independently of underlying chronic disease, physiological consequences of cancer or cancer treatment, or depression in the subjects."

And we expressed our surprise at how few such studies had been conducted. We summarized what we found:

> "Two studies were reported in the summary of a workshop[13] (but were not found in a MedLine search as of May, 2005). In the first study, trouble retaining learned information (maze negotiation) was noted in inbred mice (not further described) six weeks after receiving a single high-dose of chemotherapy (not identified). In the second study, female rats were given five monthly cycles of chemotherapy (fluorouracil or cyclophosphamide) in doses sufficient to cause symptoms of toxicity. After recovery for 2 or 8 months, the rats were tested against control groups in the Stone 14-unit T-maze and the Morris water maze. At 2 months, the chemotherapy group was no worse than, in fact was better than, the control animals in maze performance and at 8 months, the groups were the same. Hence, there appeared to be no deleterious effect of chemotherapy treatment. A third study found that multiple intracerebroventricular injections of methotrexate to male rats, at doses sufficient to cause convulsions, produced learning and memory impairment.[56]"

Followed by: "Clearly, additional [such] studies need to be done."

Conclusion

This chapter can be concluded the same way that we concluded our review.[9] The challenges to researchers and the importance to patients remain the same:

"Chemo fog/ chemo brain (cognitive dysfunction) represents a serious concern for cancer patients undergoing or contemplating chemotherapy. However, the causal relationship between this adverse outcome and the chemotherapy per se does not appear to have been unequivocally established. Thus, patients face a dilemma: undertake the treatment and possibly suffer the (unacceptable) adverse effects, or forego the treatment and possibly fare worse. Decisions are currently being made based on

the assumption that the chemotherapy is at fault. The present [book] examines this issue and suggests that further information is sorely needed." To paraphrase *David Copperfield*, whether chemotherapy shall turn out to be the cause of chemo fog, or whether that station will be held by anything else, future research must show.

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Chapter 2

Patient's Perspective

Robert B. Raffa* and Kathleen J. Martin

Abstract

An unknown, but significant subgroup (perhaps the majority), of patients who have undergone chemotherapy treatment for their cancer report a subsequent decline in cognitive performance (e.g., difficulty in balancing a checkbook; forgetting or mixing up names of friends or relatives, etc.). The condition has been termed chemo fog, chemo brain, or some similar term to reflect the fact that the symptoms are usually difficult to describe and involve domains of cognition such as attention, concentration, memory, speed of information processing, multitasking, or ability to organize information. The deficits are reported to persist. The magnitude of the negative impact on quality of life depends, as does the condition itself, on multiple and varied factors. This chapter relates the experience of one patient.

"Honey, I found the clothes you were looking for ... they're in the freezer". Her husband says with a knowing laugh and Kathy joins him, further strengthening the bond that forms between two people who make the best of the one's slight disability. So might start a typical day for someone with chemo fog/chemo brain.

Most days, such an event would be the only one that would differentiate Kathy from the rest of us who forget where we put our car keys. It is a subtle difference and a subtle effect. The forgetting part is similar to us all, perhaps occurs more frequently, but the confusion of appliances—the freezer with the clothes dryer—is not. Welcome to the world of chemo brain or chemo fog.

When with friends, a slight slip of concentration or memory is affectionately and teasingly called an 'M' (Martin) moment. But there are also the times when a family member might get mildly frustrated: *"Oh, don't you remember, I already told you what day we are going!"*.

When asked what term she thinks best describes, or comes closest to describing, the condition, Kathy quickly says that chemo fog is a good descriptive phrase. She is just glad that there is at least some term for it, however imperfect. It was very frustrating to know that something wasn't 100% right, but that nobody else seemed to have heard of it. There is some consolation in the knowledge that it has a name.

Lest the reader get the impression that Kathy's chemo fog in any way prevents her from leading a full or fulfilling life, she is an outgoing, active, enthusiastic, extremely social and engaged wife and mother, with a large circle of friends. She is an intelligent, articulate and warm person. She likes to discuss current events, books, movies, family dynamics and her many other interests. Although family and close acquaintances notice the 'M' moments, strangers are unlikely to. In the course of an hour of intense interview, only one minor occurrence was noticed.

How does the condition manifest itself in daily life? Kathy is an avid reader. But once in awhile she might be reading a really good book and realize that she already read it. But hey, *"It is just as*

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Chemo Fog: Cancer Chemotherapy-Related Cognitive Impairment, edited by Robert B. Raffa and Ronald J. Tallarida

good the second time around". Attitude is a big part of how much, or little, impact chemo fog has on quality of life. Kathy might forget where she put her car keys, but never what they are used for or throw them away. She might find items in inappropriate places (like the extreme case of the clothes in the freezer). She might get to a room, then wonder what it was she came to get. Perhaps the biggest change is that she does not feel comfortable driving anymore. Nothing serious, but she just feels like she might get lost and she rather avoid the situation, particularly if she has her grandchildren in the car with her.

It has been about 15 years since her chemotherapy. Is the chemo fog getting worse as time goes on? No, not noticeably. Does the time of day make any difference? No, not noticeably. Are there any particular mental functions that are more noticeably affected? Yes, math. She always loved math and was quick and good at it. Known for never making a mistake, she now sometimes does. Are there times or situations in which it is/was worse? No, not noticeably, although the period of 1-2 months following her chemotherapy seemed more pronounced.

Is her present chemo fog/chemo brain attributable to chemotherapy? This is a difficult question to answer, as it is for almost every cancer survivor. Kathy had serious disease. Inflammatory breast cancer. She was given little hope of survival. Most of the others she knew in her cohort did not. She received aggressive treatment. Mastectomy, radiation, bone marrow transplant, adriamycin, cyclophosphamide, 5-FU, methotrexate and along the way amphotericin B, demerol and a host of other drugs. She twice went into anaphylactic shock. She had blood clots. She had some convulsions.

So was it only the chemo, only some other factor, or some combination that led to this survivor's chemo fog/chemo brain? That question, generalized to all survivors, motivates and forms the basis of this book.

Conclusion

When asked to describe herself in 25 words or less, Kathy does not include the word 'cancer'. Does she have residual effects from her life-threatening disease and the aggressive therapy that saved her life? Yes. She estimates a 20% loss, which sounds like a lot, but on a scale of 0 to 10 (10 being worst), how 'big a deal' is the negative impact her quality of life? Zero to 1. She had children at home, so she had to function. She concurs with the suggested analogy that it is on a par with needing glasses. Does it keep her from doing things or trying things because she is afraid that she won't be able to do them? No. Does it prevent her from having a full and fulfilling life? Absolutely not. Is there something noticeable that she might attribute to her treatment? Yes.

Such is the sum and substance of chemo fog/chemo brain. It is something not to be dismissed or to be ignored, but neither should it be exaggerated. Puzzling and difficult to define and to quantify, yet it is important to do so. No need to 'try anything' to treat it, but a safe and effective pharmacologic or other treatment would be welcome.

Chapter 3

Oncology Nurse's Perspective

Jamie S. Myers*

Abstract

Oncology nurses are increasingly recognizing the importance of chemotherapy-related cognitive impairment (CRCI) in the lives of their patients and are contributing to the state of the knowledge in this field of study. The Oncology Nursing Society has included treatment related changes in cognitive function as a priority in the 2009-2013 "Oncology Nursing Society Research Agenda and Priorities". Related educational programming has been included at national nursing symposia. A brief review of some research conducted by oncology nurses is described.

Introduction: Personal Reflections of an Oncology Nurse

After 20 years of advanced nursing practice in oncology I left the acute care setting to pursue a role in the pharmaceutical industry. Shortly following this transition I became aware of CRCI. I attended an annual symposium of the Metro Denver Chapter of the ONS and was privileged to hear a presentation by a neuropsychologist, a research nurse and a former intensive care nurse who was a survivor of breast cancer. The poignant story related by the former intensive care nurse opened my eyes to CRCI. This former nurse was no longer able to work because she could no longer make sound clinical judgments due to the significant cognitive impairment she experienced during and following her chemotherapy for breast cancer.

Since that symposium, I have had the opportunity to interact with a number of cancer survivors, including Non-Hodgkin lymphoma, breast and lung cancer survivors. Common themes occurred throughout these conversations: trouble remembering numbers, difficulty multi-tasking and getting lost while driving to familiar locations. Fortunately, most of these survivors have described significant improvement in cognitive function over time. However, two described severe long-term impairment that has prevented their return to work as advanced practice nurses.

Upon hearing these stories and subsequent review of the literature on retrospective and prospective clinical trials I realized that for two decades I had developed and taught chemotherapy certification courses, administered chemotherapy and provided patient/family education without awareness of the risk for changes in cognitive function related to standard-dose treatment. As a result of this realization, I have focused my doctoral study around CRCI and am committed to adding to the body of knowledge for this serious potential sequela of chemotherapy. I am heartened by the ever-increasing literature related to this area of study and the ongoing prospective clinical trials designed to identify risk factors, causal agents and appropriate interventions.

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Chemotherapy-Related Cognitive Impairment: The Oncology Nurse Perspective

A key component of the role of the oncology nurse is the assessment and identification of treatment-related sequelae. Development of an appropriate plan of care to prevent and manage side effects includes both interventions and education of the patient and family. Estimates of the incidence of chemotherapy-related cognitive impairment (CRCI) range widely, but have been reported to be about 75-95% shortly following the completion of treatment and about 17-35% two or more years after therapy.[1] Patients acknowledge that cognitive changes significantly impact their quality of life.[1-3] Oncology nurses are increasingly recognizing the importance of CRCI in the lives of their patients and are contributing to advancing the state of the knowledge about it.

Oncology Nursing Research

Oncology Nursing Society Research Agenda

The Oncology Nursing Society (ONS) was founded in 1975 and is the leading national organization for oncology nurses. Present membership is approaching 40,000, which includes oncology nurses and ancillary oncology health care professionals with an interest in health policy and patient care. Part of the ONS mission and vision is to support the efforts of oncology nurse researchers and provide appropriate education and tools to the membership for the provision of quality cancer care. The ONS Foundation provides numerous funding opportunities to the membership for research, education and leadership development.

Results of the 2008 ONS "Research Priorities Survey" recently were published in the *Oncology Nursing Forum.*[4] ONS members were surveyed to determine the priorities of oncology nursing research and the effect of evidence-based practice resources. The results were stratified by: general membership; advanced-practice nurses; and doctorally prepared nurses. Quality of life and pain remained the top two priorities for the overall membership since 2000. Notably, doctorally prepared nurses highlighted the importance of cognitive dysfunction and symptom clusters. The results of this survey were used to construct the 2009-2013 "ONS Research Agenda and Priorities".[5] A draft of this document was presented at the ONS 10th Annual Conference on Cancer Nursing Research held in Orlando, Florida in February of 2009. Feedback was obtained from conference attendees followed by additional feedback sought from the general membership. Once finalized, the document was published on the ONS website and will be published in the *Oncology Nursing Forum*.

A high research priority is to "develop an in-depth understanding of cancer-related symptoms and side effects in children and adults across cultures and ethnicities". This priority includes developing scientific knowledge of individual or multiple symptoms and side effects to: determine causal pathways, identify short- and long-term outcomes, develop subjective and objective measures and develop/evaluate nursing interventions to prevent or ameliorate symptoms. Rationale and background include a discussion of changes in cognitive function associated with cancer therapies and the need for pretreatment evaluation of cognitive function and multidimensional neuropsychological assessment. Recommendations for future research include: description of therapy-related long-term effects on cognitive function, identification of sensitive measures of cognitive function applicable to the clinical setting, understanding of physiologic mechanisms underlying changes in cognitive function and development of appropriate interventions to ameliorate effects on cognition.[5]

An interesting area of discussion is the exploration of proinflammatory cytokine release related to the symptoms associated with sickness behavior, such as fatigue, cognitive changes, appetite suppression and decreased physical activity (the possible relationship of cytokines to chemotherapy-related cognitive impairment is considered in Chapter 16). Future research around symptom clusters also is recommended to evaluate the effectiveness of interventions. Inclusion of treatment related effects on cognitive function as an ONS research priority provides the framework to shape and support the design and implementation of future research by oncology nurses.

Selected Research Conducted by Oncology Nurses

Substantive contributions to the state of the knowledge already have been made by oncology nurses. A number of confounding factors have been identified in relationship to changes in cognitive function. Some of these include age, level of education, intelligence quotient, hormonal status, anemia, depression, anxiety, fatigue, genetic alterations and the diagnosis of cancer.[1,6-14] The results of a sample of such studies are summarized below:

- Cimprich and Ronis[15] examined differences in the cognitive capacity to direct attention (CDA) in older women newly diagnosed with breast cancer compared to healthy controls of similar age. Participants' CDA and symptom distress was measured before surgery, two weeks postoperatively and three months postoperatively. Participants in the breast cancer group scored significantly lower on CDA ($p < 0.05$) than did the healthy controls. Reduction in cognitive performance was found to persist over time in newly diagnosed older women.
- Cimprich et al[16] extended this work by examining the relationship between cognitive function prior to any treatment for breast cancer and potential confounding factors, such as age, education, menopausal status, chronic comorbidities and levels of distress. Differences between objective measures of cognitive function and self-report of cognitive changes were noted. Age and level of education were significant predictors ($p < 0.001$) of cognitive performance while symptom and mood distress predicted participants' perceptions of their own cognitive performance ($p < 0.001$).
- Bender et al[17] conducted a prospective evaluation of cognitive function in women with breast cancer who received adjuvant chemotherapy, with or without estrogen suppression, compared to those who did not receive adjuvant chemotherapy. Groups 1 and 2 were comprised of women with Stage I or II breast cancer who received chemotherapy alone vs combination therapy with tamoxifen. Group 3 was made up of women with ductal carcinoma in situ who received no adjuvant therapy. The initial evaluation time point for measures of cognitive function occurred post-operatively and prior to adjuvant therapy for Group 1 and 2 and postoperatively for Group 3 (Time 1). The second evaluation (Time 2) occurred 1 week following the conclusion of adjuvant treatment for groups 1 and 2 and at a commensurate time frame for Group 3. Time 3 was scheduled 1 year after Time 2. Adjuvant chemotherapy was shown to be associated with deterioration in verbal and working memory that persisted over time. Some indication for increased levels of cognitive change with the addition of tamoxifen to adjuvant therapy was seen. Higher depression scores were associated with greater perceptions of cognitive deficits and lack of correlation was noted between objective measures and patients' self-report. The authors suggested that future studies should include assessments at shorter time intervals, since participants' perceptions of cognitive changes were shown to precede changes in objective measures. Due to the time lapse between Time 2 and Time 3, the researchers were unable to pinpoint the precise pattern of objective cognitive decline. The results of this study provide support for the subtlety of cognitive changes that are seen in this patient population, particularly regarding participants' attempts to recall recently-learned information in situations in which there are distractions.
- Recent work by Von Ah et al[18] also compared cognitive function in breast cancer survivors to that of healthy age- and education-matched controls. Evaluation took place >1 year following completion of therapy for nonmetastatic breast cancer. Participants were assessed across a number of cognitive domains including: memory, attention and concentration, information processing speed, executive function and language. Disease and treatment characteristics as well as symptoms of depression also were assessed. Clinically significant impairment was seen in 36% of the breast cancer survivors. Recall was noted to be significantly lower for participants <4 years post treatment compared to those >4 years post treatment. The researchers suggested that time from completion of therapy may be an important variable in future studies evaluating cognitive function in breast cancer survivors.

- Myers and Teel recently conducted a pilot study to evaluate oncology nurses' awareness of CRCI.[19] A convenience sample from a Midwestern chapter of the ONS was used to conduct a survey designed to gather data about oncology nurses' awareness as well as practice patterns related to assessment and patient/family education. All participants indicated familiarity with the term chemo brain and 94% were familiar with the term 'cognitive impairment'. More than half of the participants had read professional or lay literature related to the topic and up to 40% of the participants were estimated to have experienced some degree of cognitive impairment. The majority of participants believed that CRCI occurs within 1-6 months of initiation of chemotherapy and all participants agreed that CRCI had some impact on a patient's ability to perform activities of daily living as well as at least some degree of symptom-related distress. Most participants lacked access to assessment and educational tools.
- Jansen et al conducted a meta-analysis of the sensitivity of various neuropsychological tests used to detect CRCI in patients with breast cancer.[20] Six tests were found to be sensitive to CRCI in four cognitive function domains (language, motor function, visuospatial skill and verbal memory). The tests which seemed to be the most sensitive included: grooved pegboard, Fepsy finger tapping, Rey-Osterrieth Complex Figure Test (RCFT) copy and block design subtest of the Weschler Adult Intelligence Scale (WAIS) and the language and memory subtests of the High Sensitivity Cognitive Screen (HSCS). The researchers acknowledged that many of the currently used neuropsychologic tests lack sufficient sensitivity due to detect the subtlety of CRCI in most patients.

A number of as yet unpublished studies were discussed at the recent ONS 10th Annual National Conference on Cancer Nursing Research. These included a phenomenologic study designed to evaluate the lived experience of women undergoing adjuvant therapy for breast cancer,[21] a study to examine the relationship between self-reported cognitive dysfunction and quality of life in breast cancer survivors[22] and a study evaluating chemotherapy-induced cognitive changes in breast cancer patients.[23]

Several recent review articles relevant to the topic of cancer chemotherapy-related cognitive impairment have been published in oncology nursing journals. A few of theses are highlighted below:

- Jansen et al published a critique of the literature for CRCI in women with breast cancer.[24] The cognitive domains found to be affected most frequently by CRCI in this literature review were information processing speed and motor function. The authors noted that none of the articles included a discussion of the potential risk factor of the presence of the apolipoprotein E (APOE) ε4 gene, which has been associated with decreases in cognitive function in the elderly, individuals with Alzheimer's disease and more pronounced injury from head trauma. The authors suggested the need for qualitative research methodologies to enhance the understanding of the patient experience and further work to identify valid, reliable, sensitive and specific tests to use for the measurement of CRCI.
- Jansen et al published a comprehensive review of the potential mechanisms for CRCI.[25] The discussion included information about leukoencephalopathy, cytokine-induced inflammatory response, chemotherapy-induced anemia, chemotherapy-induced menopause and genetic predisposition.
- Myers reviewed the relationship of proinflammatory cytokines to sickness behavior and cognitive impairment and provided a discussion related to the issues associated with neuropsychologic testing, neuroimaging and the role of the neuropsychologist.[26-28]
- Myers expanded on the work of Lentz et al[29,30] and Hess and Insel[31] to recommend a blending of the Theory of Unpleasant Symptoms and the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function as a framework conducive to the support of further study of CRCI.[32]
- Barton and Loprinzi suggested a number of potential interventions for future study based on results from clinical trials conducted for Alzheimer's disease and dementia. They suggested consideration of hormonal interventions, antioxidants, monoamine

oxidase inhibitors, growth factors, dopamine agonists, cholinesterase inhibitors, anti-inflammatory agents and behavioral interventions.[33]

Oncology Nursing Education

Appropriate education for oncology nurses is necessary to foster the inclusion of evidenced-based practice in assessment and identification of treatment-related sequalae and appropriate patient family education.[34] Professional organizations foster educational programming based on members' needs assessment and requests. ONS has provided a number of sessions highlighting CRCI in recent national symposia. Many institutions require specialized preparation of RNs who will be administering chemotherapy.[35] The ONS chemotherapy and biotherapy guidelines and recommendations for practice recently have been updated to include content on CRCI.[36]

Conclusion

Much work remains to be done in the study of CRCI. The majority of studies to date have focused on individuals with breast cancer. Future trials should be expanded to include other types of malignancies. Oncology nurse researchers will play a key role in the design and implementation of research to further describe the patients' experience with CRCI, the development of appropriate assessment and education tools and the evaluation of investigational interventions.

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Chapter 4

Oncology Pharmacist's Perspective

Rachel Clark-Vetri*

Abstract

The pharmacist's role places them squarely on the front line of the benefit-risk analysis of drug administration. They are often the ones who explain the drugs to the patients and, in the process, supply part of the information about which patients must make an informed decision about their chemotherapy. This chapter presents the reflections of one oncology/pain specialty pharmacist.

Over the last two decades of practicing pharmacy I have observed multiple advancements in the treatment of malignancies. For many of these treatments, higher doses or increasingly more complex combinations of antineoplastic drugs have been utilized. For a disease such as breast cancer, treatment may consist of as little as four months or as much as 5 years or more of treatment depending on the tumor characteristics and staging.[1] Patients have a certain expectation of toxicity with each type of treatment and as a pharmacist I am expected to monitor the patients for potential adverse effects. With each treatment, patients must weigh the benefit versus risk of pursuing aggressive therapy for their cancers (Fig. 1). Acute toxicities such as bone marrow suppression, nausea and vomiting and alopecia are some of the expected toxicities and patients for the most part accept these as part of using chemotherapy in the battle against cancers. Late effects such cardio toxicities and neuropathies may also be discussed as potential risks of therapy. Cognitive dysfunction or what is commonly termed "chemo fog" or "chemo brain" is not a toxicity that is usually considered prior to treatment. Part of the issue is that this phenomena although discussed in the literature, has little consensus in the medical profession as to the causality.

In my fourteen years of practicing in the oncology setting, I can only recall one patient that refused therapy because of the risk of cognitive impairment. She was a physician with an early staged breast cancer diagnosis and after careful consideration of her risk of recurrence versus the risk of cognitive impairment, decided against further adjuvant chemotherapy for her disease. The average lay person would be unaware of this sequelae and so for most patients, the decision to receive chemotherapy is based on the benefit and risk presented to them by their providers prior to treatment. Having declared that I have only had one patient refuse treatment due to the risk of cognitive impairment, I also note that I have had many patients complain of cognitive impairment after completion of their chemotherapy. Most report subtle but annoying memory loss that has little impact on their overall functioning. Forgetfulness is often described where they have trouble remembering names of people or places or they will be unable to find the right words to match their thoughts. If you ask most patients, in all probability retrospectively they would not have altered anything in regard to their treatment but most would report being uninformed of the risk prior to treatment. The fact that the cognitive impairment is not routinely discussed with the patient is partly because of the uncertainty of the

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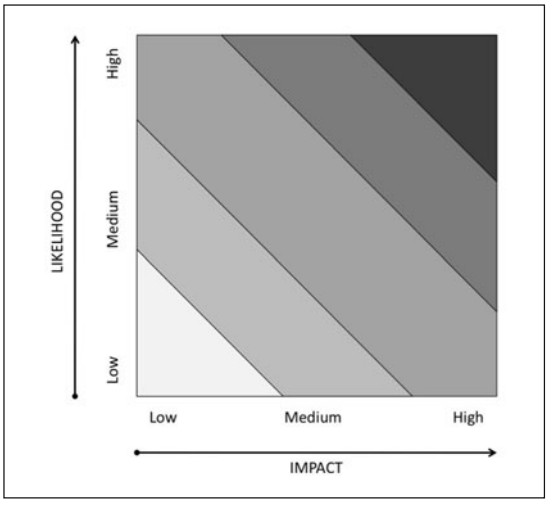

Figure 1. Benefit-risk assessment graphic. Each decision—made by each participant in the care (healthcare professional, patient and others)—must take into account both the magnitude of impact of the benefit, or risk and the likelihood that it will occur. In this graphical representation, greater negative outcome is indicated by increasingly darker shading of the regions from lower left to upper right. For any actual decision, the widths of the regions will differ and will likely differ for the individuals involved (e.g., healthcare professional vs patient, etc.).

causality, complicated by drug-related, disease-related or another biologic reason such as changes in hormone status. We certainly have no doubt that hair loss and bone marrow suppression are treatment related toxicities, but chemo fog is much more uncertain.

Predicting toxicity in the individual patient is difficult and so prior to administrating the drugs, each patient is consented to treatment in that the patient is informed of the possible risks and possible benefits of the therapy and being ware of the side effects and possible benefits, the patient consents to receive the treatment. This is true for all potential adverse effects regardless of incidence. For example if the patient will be receiving a regimen that has a less than 1% chance of congestive heart failure and an 80% chance of neutropenia the patient is told of each potential side effect with the caveat that neutropenia is much more likely to occur, but congestive heart is much more likely to be permanent. The question comes to mind that if we can anticipate a percent of patients or perhaps a subset of patients at risk of cognitive impairment relating to treatment and this side effect may be permanent, then should we be consenting patients for this possible adverse event? Regardless of the causality, I believe that patients should be made aware of the potential so that they can make better informed choice with regard to treatment. True informed consent is based on receiving adequate information for decision-making including potential risks and benefits and alternatives to treatment.

Conclusion

I believe most would concede that cognitive dysfunction is an expected side effect in some patients receiving chemotherapy although the causality is still unknown. More research in this area will hopefully answer some of these questions. In the meantime, patients should be made aware of the potential side effect and pharmacists should monitor for the adverse effect and educate patients of the potential risk. Only with all the information, can patients make a true informed consent regarding therapy.

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Chapter 5

The Impact of Chemo Brain on the Patient with a High-Grade Glioma

Michele R. Lucas*

Abstract

Health-related quality of life for patients with high-grade gliomas has always been poor. The multiple insults to the brain—tumor existence and surgical procedures, irradiation, the level of stress and anxiety suffered and the adjuvant medications—steroids and anti-convulsants, all combine to diminish their health-related quality of life. Prior to the development of chemotherapy agents capable of penetrating the blood brain barrier, prognosis was 6 to 18 months. Life expectancy was short and there was little time to address the health-related quality of life. The newer agents have served to extend life, but have added another condition to the existing poor health-related quality of life, i.e., chemo brain. Chemo brain affects all cognitive function. The patients have great difficulty processing information. They have reduced attentional and concentration capability and cannot learn new information. The overall impact on their lives renders them unemployable and places a great burden on their families and on society. This chapter provides an overview of the patient experience and the burden placed on their families and on society.

Background

A glioma is the most common type of brain tumor. It is a primary brain tumor, i.e., it originates in the brain. It does not come from a peripheral source (e.g., metastasis). Approximately 20,000 are diagnosed in the United States each year. Gliomas can be classified as shown in Figure 1.

Early chemotherapy agents were not beneficial in treating brain tumors because of their inability to penetrate the blood-brain barrier. Irradiation was the frontline treatment but chemotherapy continued to be prescribed post irradiation, as there was no other treatment available. But, with the development of improved agents that can penetrate the blood-brain barrier, it has become a significant part of the standard of care practiced worldwide and has been beneficial in extending length of life.

Care plans can vary somewhat for patients with World Health Organization Grade 3 and 4 tumors (WHO III/IV, IV/IV) but the majority will receive irradiation. Most of the patients with Grade 4 tumors will receive irradiation with concurrent chemotherapy. The chemotherapy is now given concurrently, as the irradiation allows for improved chemotherapy entry into the brain. However, it also allows for greater impact to the healthy brain tissue, thus causing chemo brain.

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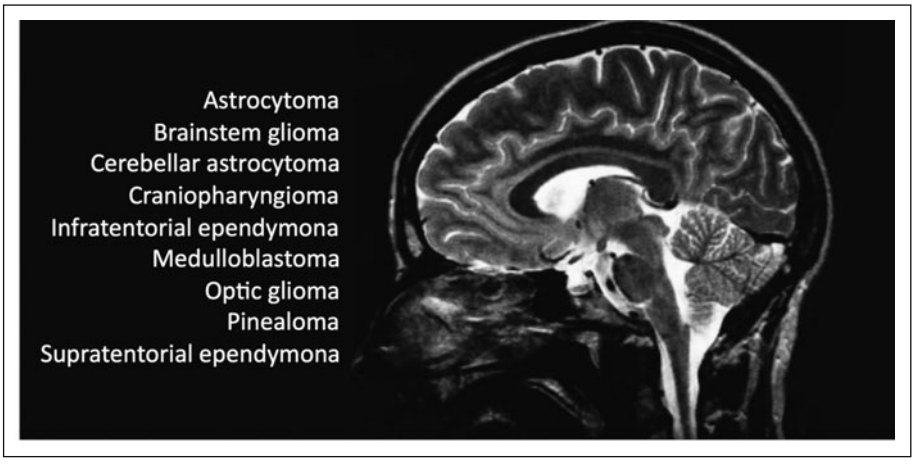

Figure 1. Types of gliomas: Astrocytomas—tumors derived from astrocytes (connective tissue cells); can be found anywhere in the brain or spinal cord; can be subdivided into 'high-grade' (the most malignant of brain tumors) or 'low-grade'; further classification can be based on the presenting signs, symptoms, treatment and prognosis, or location (the most common is cerebellum). Patients usually have increased intracranial pressure, headache and vomiting. There can also be problems with walking and coordination and double vision. Brainstem gliomas—most of these tumors cannot be surgically removed because of the location and critical function this area. Ependymomas—glial cell tumors that usually develop in the lining of the brain ventricles or in the spinal cord; can be slow growing, but may recur after treatment (more invasive with more resistance to treatment). Optic nerve gliomas—frequently occur in people with a predisposition for developing brain tumors; typically difficult to treat due to the surrounding sensitive brain structures.

Brain Cancer

Brain cancer is very different from cancer in other locations of the body because it affects thinking and information processing. It could be described as having both cancer and Alzheimer's disease, or cancer and brain injury, because of the dramatic changes that occur in the individual. And, because of this, it is not an individual's diagnosis, but that of a family unit, with major consequences to the entire unit.

Patients and their families find themselves in a state of shock and despair upon hearing the diagnosis of a malignant brain tumor. They try to be hopeful and believe the best, but are burdened by the fears of disability and, ultimately, death of the patient. The waiting to begin treatment, post diagnosis, can be the most difficult period of all because they feel totally helpless during that time. Once treatment begins there is a feeling of empowerment in knowing that everything that can be, is being, done to fight the ravages of the disease. The family unit enters into a period of sustained survival mode. During the first few months adrenaline flows and they find the strength to continue and remain hopeful. In those first few months, when radiation is being provided daily, there is little time to process the consequences of the diagnosis to the future. Internalization of the consequences begins after the fact. This is the beginning of the family unit's recognition of how life has changed. The pace of care and treatment slows and the support of family and friends declines and a new reality is established. The continued treatment is chemotherapy, administered a variety of ways: orally 5 days out of 28, 3 weeks on and 1 week off, or daily, or intravenously on a schedule determined by a study or an off study care plan. Additionally, patients are scheduled for MRI's every 2 to 3 months, with some variation specific to studies. Patients and their families then begin living in increments of time between

the scans. The prescan anxiety generally begins about a week before the appointment. The wait for the result is excruciating, as all depends on the outcome. There is no cure for this disease so they hope for a result indicating that the tumor is stable, meaning that it has not continued to grow. On occasion there is a reduction in the size and they are overjoyed. This is, unfortunately, generally meaningless in terms of overall survival, but it makes for a rare happy moment for the family unit.

Impact of Chemo Brain on the Patient

Chemo brain is the result of the toxic impact of chemotherapy on healthy brain tissue causing impairment to organizational and initiation ability, executive function and information processing speed. Daily life can vary for patients with chemo brain impairment. Some are able to continue working for some period of time, but they are in the minority. Others can do little more than exist at home. Even those who can continue to work, express great difficulty in doing so. They complain of exhaustion, not only secondary to the effects of the irradiation, but also to the energy it takes to do anything cerebral. For both sets, everything takes great deliberation. Nothing comes easily. Nothing is spontaneous. Every task, no matter how menial, can be overwhelming. For people who are tumor free, every reaction is natural and flows freely, but for the patient with a cognitive impairment, everything is broken down into parts. The example I use to help family unit's understand is as follows:

> There is a knock at the door. The normal reaction is to get up and answer it or to yell out "come in". But, for the impaired patient, it is not so simple. "I heard a noise. What was that? What does it mean? Oh, someone's at the door. I guess I should get up. Okay, I'll stand. Now I should walk toward the door. Yes, that's what I'll do. And so on and so on.

I have used this example with patients, as well, prefacing by saying I know this is going to be a gross exaggeration, but see if it is somewhat close to your experience. Over and over, patients have corrected me and said it is not an exaggeration, but exactly how they respond and react to everything in their lives now.

Due to this processing delay, they have great difficulty negotiating the world. They complain of being over-stimulated. They describe a world full of noise and rapid movement that they neither tolerate nor interpret. They are not able to shop or go to restaurants or movies. Saddest of all is the intolerance for family functions. The patient struggles to avoid any large grouping of people, thus eliminating their attendance at family gatherings (e.g., birthdays, anniversaries, holidays, etc.). They cannot engage in conversations with multiple participants. By the time they process one statement, many others have occurred and they are totally lost. And they are unable to hold onto whatever it is they might wish to say, if not allowed to say it immediately. It is too confusing for them and they prefer to avoid these occasions altogether.

They no longer trust their judgment and agonize over every reaction and decision. This causes a heightened sense of vigilance, a hyper-vigilance, that overshadows every aspect of their lives. They feel vulnerable and are fearful of scrutiny. They do all they can to avoid exposure and potential humiliation. They try to live up to others expectations to the point of exhaustion, but for most the pressure is too great and they retreat into themselves and further isolate from family and friends.

Consciously or unconsciously, most of us have adopted techniques to help soothe ourselves when we are under stress or are anxious—our personal self-maintenance techniques. Some run, some bike, fish, read, watch movies, or play computer games. However, when clearly needed the most, the high-grade gliomas patient cannot access their personal technique. They lack the ability to initiate. They cannot self start. This inability leaves them locked in boredom and despair. Even if handed a book, they might not be able to retain what they read and need to read the same page over and over. Or they may not have the attention span to watch a movie and, if they can watch it, may not have any memory of it shortly after.

Impact of Chemo Brain on the Family

The vast majority of family units suffer a decline in income just as treatment increases expenditures. The significance of the loss is, of course, dependent on the age and earning capacity of the patient. If the patient is the major wage earner, the decline in income can be devastating. Even if the patient has short and/or long term disability benefits, the income is generally only a percentage of the original amount. Some are eligible for Social Security Disability Income (SSDI), but this too can be a dramatic decrease.

Due to the disability of the patient, families must make arrangements for someone to stay with them at all times, to keep them from harm. This may be simple to do or extremely complex. One member may stop working by quitting, retiring, or taking an unpaid leave, or the choice may be to hire a professional caretaker. Whichever way, there is a substantial cost to the family resulting in diminished financial resources.

Over time—during which mutual support is needed the most—the patient is incapable of considering the needs of their spouse, their parents and/or their children. They may have no awareness due to their neuro-degeneration. They become totally consumed with their own self-maintenance. They do frequently express feelings of guilt for burdening the family unit but do not have the capacity to reverse it. The family unit is left assuming all responsibilities. The intimacy once shared by couples is non-existent. Children are left wondering about their relationship with a parent who cannot participate in their lives. There is strain on every relationship.

Particularly painful is the invisibility of the disease once the scar heals and the hair grows back. The majority of patients then look just as they did before diagnosis. Extended family and friends, those who do not live with the patients and witness daily how compromised they are, begin to believe they have been restored to their former selves. They withdraw the assistance and support that the family unit so desperately needs. The invisibility is confusing for young children, in particular, as daddy or mommy must be all better as they look fine, but continue to be impatient and intolerant because they are overwhelmed by children's rapid chatter and movement. Teens, who are so often consumed and driven in their need to challenge their family's beliefs and rules, frequently rebel and act out, adding another layer of suffering and pain for the family unit. The healthy spouse is caught between the needs of the patient and the children. And, in their exhaustion, they, too, frequently become impatient with the patient because they look fully capable but have no insight, behave badly and ask the same question over and over.

Due to the patient's inability to function in social settings, the entire family is forced to live the life of a sick person. They must forego opportunities for interaction and support when most needed.

Impact of Chemo Brain on Society

As the majority of patients are too cognitively impaired to work and generate income, their contribution to the work force and their independence is lost. They become dependent on society by utilizing income and health insurance benefits, resources from state and federal programs and charity from nonprofit organizations. If the spouse or primary caretaker has to leave work, they too may become dependent on society for survival. The longer the dependent patient lives, the greater the financial drain on all sources.

Healthcare costs rise not only for the patient but potentially for the entire family unit. There is frequently a need for mental health counseling for members of the family unit in reaction to the dramatic changes that the family unit undergoes. Primary caregivers are vulnerable to increased illness due to the weakening of their immune system in reaction to the weight of the anxiety and stress and the exhaustion they endure in the caretaking role.

It is not unusual, when the life of the patient is extended beyond a few years, to see a family unit fully dependent on income from Social Security disability income, government indigency programs that provide food stamps, plus, pharmaceutical indigency programs, reduced cost fuel programs and Medicare and/or Medicaid.

Conclusion

The introduction of chemotherapy agents that can penetrate the blood-brain barrier in treating the high-grade glioma patient has proven instrumental in extending life. However, the extension appears to be of no benefit to the patient regarding their health-related quality of life. In fact, as time passes, the chemotherapy treatment, in combination with the long term effects of the previous insults to the brain, cause progression in their neuro-degenerative decline. The patient lingers longer in a compromised condition, extending their despair and extending the family unit's emotional and financial predicament. Further attention must be given to the implications of penetration of the blood-brain barrier.

In the interim, more attention must be devoted to the development and accessibility of rehabilitation and support services for the patient and family unit. Although patients are generally incapable of being self-analytical, success has been seen with the use of modified cognitive behavioral programs, similar to those utilized in treating head injury patients. Additionally, the family unit needs to have their experience normalized and validated. They need ongoing supportive counseling and the services of financial counselors to help direct them through the maze of diminished income, healthcare costs and insurance companies.

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Chapter 6

Neurocognitive Effects of Childhood Cancer Treatment

Jennifer Costa*

Abstract

With changes in the approach to treatment of childhood leukemia and brain tumors, more children are surviving into adulthood. With this increase in long-term survivorship, long-term neurocognitive side effects have emerged. Research has shown that these survivors suffer a variety of neurocognitive effects including changes in attention span, concentration, school performance and executive functioning. Researchers continue to study changes in therapy with the hopes of decreasing these long-term side effects without compromising overall survival rates. Others have focused on developing adaptations to how these children learn, equipping them with tools to better cope with learning deficits. Still, others have looked into pharmacological interventions. This chapter will discuss the historical course of therapy for both leukemia and brain tumors. In addition, it will highlight how late effect studies guided changes in therapeutic approach for both childhood leukemias and brain tumors. This chapter will also discuss specific neurocognitive effects from childhood cancer treatment, challenges in research methodologies as well as current pharmacological and nonpharmacological interventions for affected childhood cancer survivors.

Background

Although uncommon, cancer is the second leading cause of death in children, exceeded only by accidents. On average, 1 to 2 children develop cancer each year for every 10,000 children in the United States. In the United States in 2009, approximately 10,730 children under age 14 are expected to be diagnosed with cancer. Leukemia and cancers of the brain and central nervous system account for more than half of the new cases (Fig. 1).[1] The most common solid tumors are brain tumors.[1] It is expected that about 1,380 children will die from the disease, one-third of these deaths being from leukemia.[1] Over the past 30 years, advances in technology and research has markedly improved 5-year relative survival rates for all childhood cancers combined from less than 50% before the 1970s to 80% today (Fig. 2). Besides advances in technology and research, the substantial progress in pediatric cancer survival rates is also attributable largely to improved treatments and the high proportion of patients participating in clinical trials.[1]

Although survival rates vary extremely from one type of cancer to another, it is well known that survivors of childhood cancers may experience treatment related side effects. Late effects include organ malfunction, secondary cancers and cognitive impairments. Cognitive impairments for children treated for leukemia and brain tumors are believed to be secondary to the multi-modal treatment approach. With the increasing number of childhood cancer survivors, it has become

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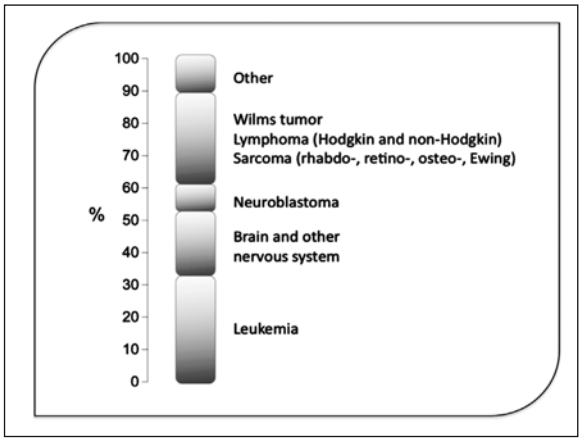

Figure 1. Classification and percentage by type of childhood cancers.

increasingly important to understand the effects of therapy in brain development to predict risks for survivors and choose optimal treatment strategies for those newly diagnosed.[2]

Identified Risk Factors

Since the late 1970s, researchers have been examining the neurocognitive late effects of childhood cancers. Much of their research has focused on those children who had experienced a clear insult to the brain from a brain tumor and/or cranial irradiation since these populations would likely be the ones with the most obvious late effects. Their research proved that chemotherapy and irradiation did indeed cause declines in overall academic function and intelligence. Many factors were examined including age, sex, diagnosis and therapy modalities. Studies in both leukemia and brain tumors emerged with indicators of relative risk factors in the likelihood of developing increased neuropsychological dysfunction following central nervous system (CNS) directed therapy.

Children diagnosed with leukemias or brain tumors are at the greatest risk of developing treatment-related neurocognitive deficits. Children at higher risk for cognitive sequelae include

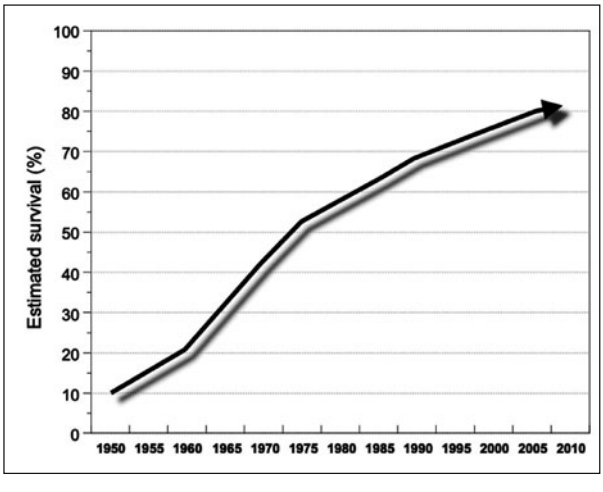

Figure 2. Improvement in survival from childhood cancer.

those younger than 6 to 8 years old, particularly females;[3] those who received central nervous system radiation;[3] and those with a combination of these two factors. In addition, children receiving concurrent intrathecal methotrexate or high-dose intravenous methotrexate and those with computerized axial tomography scan abnormalities have additional risk factors for cognitive sequelae.[3] Finally, it has been noted that those children receiving intrathecal or systemic chemotherapy[4] and/or cranial radiation greater than or equal to 1800 cGy also experience neurocognitive deficits.[3]

Treatment of Childhood Leukemia: Past and Present

By the 1950s and 1960s, organized chemotherapy protocols began to emerge and the length of survival in children with leukemia began to increase. However, these children almost inevitably relapsed, most often in the CNS.[5] It was at this time that researchers began to recognize that leukemic cells are able to cross the blood brain barrier and are present in the meninges early in the course of the disease. At that time, 80% of children not treated with therapy specifically directed to the CNS developed CNS leukemia.[6] As a result, CNS directed therapies emerged, dramatically increasing survival.[5] In the early 1970s, CNS prophylaxis consisted initially of 2400 cGy radiation to the neuroaxis. Later 2400 cGy cranial radiation was combined with intrathecally administered methotrexate. Although CNS leukemic infiltrates were being targeted and treated and survival rates of children with leukemia increased to about 80%, toxic side effects of CNS directed therapy soon became apparent.

The first cohort of long-term childhood leukemia survivors began to emerge in the late 1970s. Within this cohort, significant neurocognitive deficits, specifically declines in intellectual functioning in younger children, soon became apparent.[7] Side effects of CNS irradiation included neurological complications, growth inhibition and second malignancies. By the 1980s, these reports on the neurotoxicity and adverse cognitive effects of these combination treatments led to the implication of prophylactic cranial radiation as the agent responsible for long-term neurocognitive effects and academic deficits among survivors.[8] Efforts were made to reduce the amount of cranial radiation doses to decrease toxic side effects while not increasing CNS relapse rates. It was later realized that the once optimistic finding of decreasing radiation doses from 2400-1800 cGy and decrease in long-term effects was no longer founded. Detrimental effects of cranial radiation on intellectual functioning remained despite reduction of radiation dose from 2400 cGy to 1800 cGy.[9]

Recognizing the link of cranial radiation and neurocognitive effects, new therapy regimens began to look at the results of eradicating cranial radiation therapy altogether. In current pediatric leukemia treatment protocols, children are stratified according to an understood risk of relapse. Low and standard risk patients typically receive chemotherapy only regimens with cranial radiation being reserved for the 2-20% of patients considered as high risk for CNS relapse.[10] In most leukemia treatment protocols today, cranial radiation has been replaced by other modalities of chemotherapy. To address subclinical leukemic infiltration of the CNS, intrathecal therapy consisting of methotrexate alone or of triple intrathecal therapy (Methotrexate, Cytarabine and Hydrocortisone) is utilized. In addition, utilization of systemic chemotherapy, specifically high dose intravenous methotrexate and systemic corticosteroids, which both have permeation through the blood brain barrier, has been a vital part of preventing CNS relapse.

Treatment of Childhood Brain Tumors: Past and Present

The other group of pediatric cancers that receive a direct insult to the brain from therapy are brain tumors. Unfortunately, children with brain tumors generally do not share the favorable prognosis of those with other childhood cancers like leukemia. Medulloblastoma, the most common malignant tumor in childhood, has a long-term survival rate of 65% while children with intrinsic brain stem gliomas have a less than 10% chance of survival.[11] However, like leukemia, improvements in the treatment of brain tumors over time has resulted in a decline in mortality rate of 23% between 1975 and 1995, with a 5-year relative survival rate of approximately 65%.

With brain tumors, treatment regimens vary depending on tumor histology and location.[11] However, treatment typically consists of a combination of surgery and local or craniospinal

radiation with or without adjuvant chemotherapy.[11] Brain tumors are a heterogeneous mix of tumors with a wide variety of treatments and outcomes. They require aggressive, multi-modal therapy which in turn leads to significant long-term difficulties and late effects. Multimodal therapy includes consideration and utilization of radiation, surgery and chemotherapy.

Surgical resection or biopsy of the brain tumor is the first step in the treatment of childhood brain tumors. Careful planning and imaging are essential prior to performing surgery in order to most accurately define location and borders of the tumor. The goal of a surgical resection is to remove as much tumor as possible while preserving neurological function. A child will often experience symptomatic relief after tumor resection. For some brain tumors, the degree of original surgical resection can affect final prognosis.[12]

Radiation therapy, in conjunction with surgical resection, has been used in children with brain tumors since the 1930s and has long been the gold standard for treating brain tumors. However, radiation to developing brains has always been a concern to those directing therapy for a child with a brain tumor. During the late 1980s and early 1990s, many trials were done to minimize or even avoid radiation therapy in children less than 5 years old. These trials investigated the use of more intensive surgery or even myeloablative chemotherapy with bone marrow rescue. Unfortunately, many of these children developed recurrent tumors without much improvement in survival. As a result much work has been done to minimize the dose and extent of radiation for children with brain tumors, especially those children less than five years old.[12] Utilization of stereotactic radiotherapy and hyperfractionated radiation therapy are just two techniques used to minimize damage to normal tissue in the radiation field.[12]

Chemotherapy is another essential therapy included in the multimodal approach to treating brain tumors. It is important in the treatment of the very young children with brain tumors as it is often used to avoid or delay radiation therapy that can be harmful to developing brains. In addition, certain chemotherapies can cross the tight blood-brain barrier that protects the brain.[12]

Neurocognitive Effects of Chemotherapy

As a result of CNS-directed therapies in both leukemia and brain tumors, children are at risk for developing neurocognitive late effects. The literature indicates that the most common neuropsychological effects of treatment involve deficits in visual processing, visual-motor functioning, attention and executive functioning (Table 1). Difficulties in visual processing affect how a child makes sense out of visual information. For example, they may have difficulty understanding maps or being shown something without verbal explanation. Visual-motor functioning involves skills like legibility of handwriting and the ability to copy drawings. Attention refers to a child's ability to maintain concentration of focus and ignore distractions. Finally, executive functioning refers to the ability to organize, plan, hold information in one's mind, manipulate it and self-monitor behavior. Some studies have also found minor difficulties in verbal abilities, memory and academic achievement. Between one quarter and one-third of subjects show some neurocognitive decline regardless of specific chemotherapy protocol. It has also been noted that girls are more affected than boys and younger children, particularly those less than 3 years old have greater deficits.[2] Some childhood cancer survivors have also suffered declines in intellectual and academic achievement. The most common deficits observed have been in memory, attention/concentration, sequencing, processing speed, visual perceptual ability and language.[11]

There is a large amount of literature documenting the various areas/types of neurocognitive deficits related to therapy for pediatric cancers. Unfortunately, methodological issues complicate the literature on neurocognitive outcomes for pediatric cancers and its treatment. Foundational studies of 1975-1980 showed cognitive declines in survivors of childhood leukemia by measurement of intelligence and academic achievement. Intelligence and academic achievement tests are relatively insensitive to specific neuropsychological impairments. As a result, it is possible that functional deficits, as well as strengths, exist that are not being properly assessed.[11] Nevertheless, the benefit of theses early studies include the identification of risk factors with CNS directed therapies. In addition, these historical, preliminary studies laid the foundation for later definitive

Table 1. Common neuropsychological effects of CNS-directed therapies for leukemia and brain tumors in children

Function	Deficit	Examples
Visual processing	Less able to make sense of visual information	Difficulty understanding maps or might require verbal explanation of objects
Visual-motor function	Reduced eye-hand coordination	Reduced legibility of handwriting or inability to accurately copy drawings
Attention	Decreased ability to maintain concentration and to ignore distractions	Inattentiveness in classroom, apparent disinterest in reading, etc.
Executive function	Decreased ability to organize, plan and hold information, manipulate it and self-monitor behavior	Difficulty getting started or finishing work, remembering homework, memorizing facts, writing essays or reports, working math problems, being on time, controlling emotions, completing long-term projects, or planning for the future

research. More commonly now, studies focus on the more discreet neuropsychological deficits associated with treatment effects for leukemias and brain tumors. These studies examine attention spans, ability to concentrate, degree of distractibility, school performance, more specifically in arithmetic performance.

There are a number of other issues to consider when evaluating research on the neurocognitive effects of cancer therapies in children. As alluded to previously, neurocognitive tests vary widely from one study to the next and are frequently updated. This makes it difficult to see a replication of findings. In addition, treatment protocols are also constantly being updated. Therefore, even if a study focuses on one protocol, it is often quickly obsolete. It is also impossible to determine the effects of any single chemotherapy agent because they are rarely administered alone. Additionally, it is also difficult to separate out the effects of the disease from the effects of treatment as healthy patients do not receive these treatments. Despite these limitations, research in this area is progressing toward a better understanding of the effects of chemotherapy on children's brains.[2]

Cognitive Remediation

It is clear that both survivors of childhood leukemias and brain tumors share many of the same cognitive difficulties after therapy. Recognizing this, there has been an interest in developing effective learning strategies through a process called cognitive remediation. Butler and Copeland have been at the forefront of developing and applying cognitive remediation principles to children who have developed neurocognitive deficits as a result of cancer treatment.[13] Butler and Copeland have developed a remedial program very similar to cognitive retraining systems proven successful in adults with brain injuries. Their remedial program is designed to equip these affected children with proper, effective and proven learning strategies. Their framework uses a tripartite model that incorporates three disciplines: brain injury rehabilitation, special education/educational psychology and clinical psychology.

Use of a tripartite model builds the foundation of Butler and Copeland's cognitive remediation program. However, unique to the program is that the developed cognitive behavioral methods are specifically directed toward the ability to withstand distraction. Children practice

how to overtly talk oneself through a distracting experience, thus enabling them to maintain attention and concentration. It is expected that with coaching, the child's self-directed overt dialogue can be internalized, thus allowing the child to use it covertly.[13] By incorporating a cognitive behavioral approach, Butler and Copeland's cognitive remediation program ensures a realistic, positive and optimistic learning environment for the child.

It is important to acknowledge that these cognitive deficits may not appear until 2 to 3 years after treatment and the degree of late effects differs from child to child. Children who are not integrated into a formal remediation program risk developing ineffective learning strategies and long-term learning disabilities. Children integrated into formal remediation programs learn appropriate and effective learning techniques.[13,3]

Cognitive remediation programs are critical to the future academic achievement, social adjustment and success of at-risk children. Successful completion of cognitive remediation programs ensures that children will not only be better able to focus on tasks and process information but also be able to maintain organization and successfully multitask in everyday life. The emergence of cognitive remediation programs to counter the neurocognitive late effects should become the standard of care for at-risk patients.

Pharmacological Intervention: Methylphenidate

In examining some of the neurocognitive late effects experienced by survivors of childhood leukemia and brain tumors, researchers have noted that these populations exhibit similar symptoms of those children with attention deficit hyperactivity disorder (ADHD) primarily of the inattentive sub-type. Recognizing this, numerous research studies have been created and are currently recruiting participants to examine the efficacy of pharmacological intervention, specifically methylphenidate (MPH), a common drug used for children with ADHD.

Early results show that methylphenidate might at least temporarily reduce some attentional and social deficits among survivors of childhood leukemia and brain tumors.[14] It has been shown to improve performance on one measure of attention, cognitive flexibility and processing speed (Stroop Word-Color Association Test).[15] In one study, male gender, older age at treatment and higher intelligence were predictive of better response to MPH. No significant differences were found for number or severity of adverse side effects as a function of active medication. It may be concluded that MPH shows some neurocognitive benefit and is well tolerated by the majority of children surviving leukemia and brain tumors. Future studies need to be conducted to establish further validity of MPH and other pharmacological agents in mediation of neurocognitive late effects in childhood leukemia and brain tumor survivors.

Conclusion

With the increase in the long-term survivors of childhood leukemias and brain tumors, it is essential to address the reality that many of these children and young adults may experience neurocognitive late effects related to the therapy they received. In order to fully utilize and integrate future research, it is essential for study methodologies to be consistent amongst the research. With consistency in methodologies, data can more accurately be evaluated and more defined conclusions can be made. Research will focus on more accurately defining and understanding the exact neurocognitive deficits that accompany childhood leukemias and brain tumors. Enrollment of children into organized treatment protocols will continue and therapies will be amended to promote increased survival with decreased late effects. In addition to modifying therapies, new directions in integrating innovative pharmacological and nonpharmacological methods of improving attentional processes and neurocognitive functioning will be essential. It is undeniable that there is still much work to be done in this area; however, patients, families, health care professionals and researchers can be optimistic of what is to come in the future.

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Chapter 7

The Economic Burden

Albert I. Wertheimer*

Abstract

Not only is chemo fog a troublesome medical problem for the sufferers, but in addition it is the source of nearly $300 million in direct and indirect expense in the United States alone each year. And since it often persists for extended periods of time, the indirect costs, which stem mainly from lost productivity, continue to accumulate with another nearly $250 million added to the overall cost each year. This is not the highest economic burden for common diseases, but it is a significant amount that could be mostly avoided if biomedical scientists were to find a means to employ safer chemotherapeutic agents.

Epidemiology of Chemo Fog

Approximately 180,000 new cases of breast cancer are diagnosed annually in the United States.[1] Breast cancer affects up to one in 10 women in Western countries and fortunately, the majority of these women are cured of the disease by a combination of early diagnosis, surgery and systemic adjuvant therapy. In fact this strategy has been so successful, that it is estimated that there were about 2.4 million women with a history of breast cancer who were alive in January, 2004 in the United States,[2] and the number is growing. Recently, it has become recognized that a possible side effect from adjuvant (chemotherapy) therapy is the impairment of cognitive function. Cognitive function is a prerequisite of functioning in contemporary daily life and therefore this is a major, significant problem.[3]

The interest in cognitive impairment as a result of chemotherapy continues to grow and the condition has been given the names of "chemo fog" and "chemo brain". Some of the symptoms of this problem include lack of the ability to concentrate, short-term memory loss, fatigue, depression, attention deficits, feeling of confusion, mental fogginess, forgetfulness and the inability to focus. Today, the existence of this chemo brain phenomenon is widely accepted even though many of the details of the concept are controversial and exact mechanisms remain unknown.[4] Mild cognitive impairment may be as minor as a mere nuisance; more severe cases can impede the work of persons who require high levels of intellectual involvement.

Conventional chemotherapy employs taxanes, vinca alkaloids, platinum compounds, cytarabine and thalidomide, among others. These compounds are known to have some neurotoxicity. Some newer chemotherapeutic agents include capecitabine, bortezomib and others, but it appears that each drug and combinations employed against breast and other cancers is currently suspect, albeit not proven, to have negative cognitive effect.[5]

The problem continues to gain the attention of researchers and the first international workshop on cognitive function in adult cancer survivors was held in Canada in 2003. A second workshop was held in October 2006 in Venice and today researchers are looking at cognitive function as related to numerous other cancers beside that of the breast. Hormonal therapy and radiation are

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also believed to have negative impact, but they do not approach the magnitude of the problem caused by the wide use of chemotherapy. One report indicated that cognitive impairment is between 15% and 50% of adult solid tumor survivors who had received chemotherapy.[6]

Unfortunately, no treatment to date has been proposed or developed for this problem despite large numbers of cancer patients who report this posttreatment memory dysfunction. A number of studies report this impairment lasting more than five or even 10 years and in some cases for the rest of the patient's life.[7]

Since the mechanism causing this problem is still unknown, little progress has been made in developing treatments. Some of the agents that have been tried and which may show some positive activity include: olanzapine and donezepril, hormones, antioxidants, monoamine oxidase inhibitors, growth factors, dopamine agonists, cholinesterase inhibitors and anti-inflammatory agents.[4]

Disease Impact

It is clear that this could be a medical condition that is widespread and potentially having serious consequences. A medical problem may be described in several ways. In clinical terms, one may refer to the prevalence, or the number of cases or patients who have this condition or to the incidents which describes how many new cases are seen or diagnosed every week, month or year. Economists look at what is called the burden of a disease which is simply stated as the total costs that are a result of the total population of patients with a specified condition. These costs generally fit into one of two categories; *direct costs* are usually in the treatment costs which would include hospitals, doctors, pharmaceuticals, diagnostic and laboratory services, psychologists and custodial care, to name several.

The *indirect costs* would include the expense for transportation from one's home to the clinic or hospital, parking, perhaps lodging of a family member near the hospital as well as meals consumed outside the home and a usually very large component called *lost productivity*. This productivity loss may be a combination of the productivity loss of the patient as well as that of those who are staying with or visiting the patient. The direct and indirect costs are added together and the some of those two categories for all of the persons suffering from bad condition becomes the figure referred to as the *burden of illness*.

We have a serious problem in calculating the burden of illness for chemo fog. As was stated earlier, there are no accepted treatments, there are no known preventive measures and it does not appear that screening is possible to determine who might be most severely affected, at least to date. There are other disease entities where the indirect costs often outweigh the direct costs. The example usually given is that of asthma, where the patient, often a child, requires that one parent stay home from work in order to care for that patient when the condition has exacerbations. The direct cost for the asthma treatment normally involves the use of an inhaler and some oral medication, which are not particularly costly. However, the lost productivity at work is usually far in excess of the medication cost.

Other conditions that have atypical cost characteristics include depression where depressed patients sense a higher number of medical conditions requiring treatment than do nondepressed patients and also lose work time.

Economic Burden of Chemo Fog

This section will be constructed based upon a number of assumptions that are subject to interpretation and a large number of estimates which are not warranted to be precise. Nevertheless, this calculation to determine the economic burden of chemo fog in the United States during a typical year will give us a reasonable approximation for the cost to society from the existence of this medical condition. A typical pharmaco-economic evaluation would name the perspective from which the study was based, but this estimation will be a more generic or general calculation that looks at all costs from all perspectives.

Direct Costs

First we will look at the direct costs and we find, as was mentioned previously, that there are 180,000 new cases of breast cancer diagnosed annually. Next we will assume that some proportion of those 180,000 patients had chemotherapy treatments as a component of their breast cancer treatment. Let us say that 60% of the patients had chemotherapy. This would give us a total population of chemo-therapy patients of 108,000.

The literature indicated that between 35% and 50% of those patients felt some cognitive ability reduction. We will use a convenient figure of 40% as a compromise. These 40% of the 108,000 patients sought care, most likely, from their oncologist regarding the recognized cognitive problem. Immediately, we have an additional office visit for each of those 43,200 patients with cognitive ability problems. Medical fees in the United States vary widely especially by geographic region and also based upon the credentials of the practitioner. Let us assume a fee of $100 for each of those 43,200 visits. This brings to our first direct expense of $4,320,000.

Now our calculation becomes a bit more imprecise. But let us invent a scenario for the purpose of demonstrating how the calculations are made (the actual values can be substituted as precise data are obtained). Let us make an assumption and say that 50% of those patients were assertive with their oncologists and wanted to get to the bottom of the problem so that their careers as lawyers, doctors, accountants, airplane pilots, etc. would not be interfered with. These 26,600 patients had appointments made for consultations with neurologists at $150 each. This adds another $3,990,000. And 75% of those neurologists ordered MRI studies at $1200 each. We have an additional cost of $23, 940,000 (19,950 pts × $1200). Not finding any identifiable pathology, these neurologists wrote prescriptions for 25% of those patients who demanded that some therapy be initiated. Those 4,987 patients began taking Aricept 5 mg tablets at a cost of $2,200 each or for a total drug burden of $10,971,400. (4987 pts × $2,200). And finally there was a second neurologists visit to review the MRI results and to determine whether the drug therapy was having any positive effect. This adds another $3,990 000. The total direct costs add up to more than 47 million dollars (see Table 1).

Indirect Costs

The vast majority of indirect costs will emanate from a loss of productivity. It is likely that there will be few absences from work, but the work might be done more slowly or may require being checked the second or third time. We will make some wild assumptions. We know that the average individual income in 2005 was $28,567.

Let us say that workers were able to only accomplish 80% of what they had previously accomplished prior to the chemotherapy treatments. On a theoretical basis, the workers with chemo fog lost 20% of their salary, or their employers 20% of income and therefore the loss is $5,713 less per year. We multiply this figure times the 43,200 newly diagnosed breast cancer patients with serious chemo fog and we arrive at an indirect cost of lost productivity of $246.8 million (see Table 2).

Table 1. Direct chemo fog costs

Item	Yearly Direct Cost (in US Dollars)
Oncologist visit	4,320,000
Neurologist visit	3,990,000
MRI scan	23,940,000
Drug (e.g., Aricept)	10,971,400
Follow-up (neurologist)	3,990,000
Total direct cost	**47,211,400**

Table 2. Indirect chemo fog costs

Item	Yearly Indirect Cost (in US Dollars)
Lost productivity	246,801,600
Total indirect cost	**246,801,600**

Table 3. Total chemo fog cost burden

Item	Yearly Cost (in US Dollars)
Direct cost	47,211,400
Indirect cost	246,801,600
Total cost	**294,013,000**

Total Burden

Based on the very rough nature of this calculation, necessitated by the lack of data on the economics of this condition, the total US annual financial burden due to chemo fog/chemo brain may therefore be estimated at **$294,013,000** or stated more roughly, at nearly a third of a billion dollars (see Table 3).

Conclusion

Fortunately, the cognitive deficits caused in about forty percent of chemotherapy-treated breast cancer patients is not life-threatening, but it is an undesirable problem along two fronts; the awkward and potentially embarrasing reality of lost memory or impaired or reduced skills and the subject of this chapter; the economic burden of the so-called chemo fog to individual patients as well as an aggregate societal cost. Sufferers who cannot work as fast or as skillfully will have a loss of income as their productivity declines as a result of this problem creating what is the indirect cost of the problem. The direct cost is the amount of money spent on medical treatment, diagnosis, testing and pharmaceuticals in an effort to ameliorate the impact of the condition.

In the case of chemo fog and with some other particular diseases, such as asthma, for example, the indirect costs far exceed the direct costs. Nevertheless the total of these two figures are a painful burden to the individual patient as well as the society as a whole. Hopefully, future chemotherapy improvements will include the actual medications that will not cause this preventable or avoidable problem creating a therapeutic and financial benefit for all stakeholders. Such a result would have a first year, immediate savings to the society of nearly $300 million.

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Chapter 8

Designing Conceptual Model-Based Research in Chemotherapy-Related Changes in Cognitive Function

Lisa M. Hess*

Abstract

Any well-designed biobehavioral research will begin with a comprehensive understanding and stated conceptual approach to the issue to be studied and the hypotheses to be tested. Following this conceptual orientation, the research protocol can be designed. This chapter reviews these factors to guide conceptual model-based research of chemotherapy-related changes in cognitive function.

Understanding the Issue

Defining the Problem

Cognitive function is a very broad term that refers to cognitive processes. The human mind is able to perform a variety of processes, many of which are performed simultaneously and are often linked closely to one another. For example, when looking at an object, one may recall memories of the object from past experience and store the image so that it can be later recalled. That visual image may also be called upon for other cognitive functions, such as decision making or problem solving. Consider seeing a stop sign at an intersection. The cognitive activity associated with the visualization of this object, may encompass imagery, perception, memory, language, decision-making, reasoning and motor response. Researchers investigating cognitive function have a challenging task and must clearly define which aspects of cognitive function are being studied. Chemotherapy-related changes in cognitive function have primarily been studied in the domains of attention, language, visual and motor skills, processing speed, executive function, recall and memory.[1,2] Each of these domains does not simply encompass one isolated cognitive function, but are comprised of a set of more specific cognitive processes that often work together to complete tasks. For example, positron-emission tomography (PET scan) research has shown that four different types of language tasks (i.e., viewing, hearing, generating and speaking words) can be mapped to four clearly distinct parts of the brain.[3] However, in daily activities, rarely do we simply view a word without further action (e.g., verbalization, memory storage). Often, a broader set of cognitive processes is needed to successfully perform an action. The first step in developing and conducting effective research on the effects of chemotherapy on cognitive function is to carefully and clearly operationalize what is meant by cognitive function and specify the domains and processes under investigation in the study.

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Chemo Fog: Cancer Chemotherapy-Related Cognitive Impairment, edited by Robert B. Raffa and Ronald J. Tallarida

Attention is comprised of several different cognitive tasks, such as concentration, preparation to receive new information and a focus on any number of a larger set of stimuli.[4] Each of these aspects of the cognitive function domain of attention engages unique and related parts of the brain. For example, neurocognitive research has shown that the parietal cortex is activated when individuals perform cognitive attention tasks that involve visuospatial details; however, the frontal lobe of the cortex is involved when an attention task is performed that includes word recognition (e.g., Stroop test).[4] Selective versus divided attention tasks also require different sets of cognitive processes.[4] Selective attention denotes a focus on a select fact or stimulus when there are multiple sources of information being received. This is a routine activity that all humans must do to accomplish tasks and communicate with others. For example, in a crowded nightclub, one must focus on the conversation of interest and reduce the focus on background noise and other conversations. In other situations, divided attention is needed, such as for driving. While driving, one cannot only focus on the speedometer and neglect the road or nearby vehicles. Instead, one must simultaneously focus on a set of events and stimuli to accomplish the task of driving. Both forms of attention are needed for humans to effectively function in daily life and therefore demonstrate how various activities involving attention differ in the way the brain must process information. When studying the cognitive domain of attention in relation to chemotherapy-related changes in cognitive function, it is important to specifically characterize what is meant by attention, how the specific processes are thought to be impacted by chemotherapy and how these changes are to be measured.

Memory is a term that encompasses an even broader set of cognitive processes. Forms of memory addressed in the scientific literature include procedural memory (recalling how to perform a task, such as driving a car), working memory (keeping something in mind for immediate use), long-term memory (recalling events in one's distant past, such as one's childhood), episodic memory (recalling events in the more immediate past, such as what one had for breakfast), semantic memory (factual knowledge, such as the name of the first president of the U.S.) and many others.[4-6] Each form of memory can work in a different manner and may or may not improve or decline together. Conditions that are known to impact cognitive function do not all act in similar ways on the brain's functional ability. A review by Burton summarizes some of these differences: anxiety is known to impact episodic memory, but not semantic or procedural memory; depression has a strong impact on procedural memory; hypoxia-ischemia impacts episodic memory but neither semantic nor procedural memory; and Alzheimer's disease impacts episodic and semantic but not procedural memory.[6] Furthermore, distinct regions of the brain are primarily responsible for these different functions: the hippocampus and medial temporal lobe are largely responsible for episodic memory functions; procedural memory tasks have been mapped to the basal ganglia, supplementary motor area and cerebellum; and working memory is largely managed by a variety of networks, primarily in the prefrontal cortex, but also involves the frontal and parietal cortical regions and subcortical structures.[6] Working memory is more complex; it integrates activities involving attention, concentration and short-term memory and others depending on the specific task. Because of the complexity of working memory, it tends to be impacted across a broader spectrum of conditions. Working memory has been studied in many trials of chemotherapy-related cognitive function,[2,7,8] likely due to its relevance to an individual's daily functional ability, as well as the likelihood of experiencing decline due to its integration of cognitive processes.

There are many documented domains of cognitive function and these seemingly obvious terms can, in fact, describe very different things depending on what type of activity is being assessed and which cognitive processes are being utilized to perform that activity. The examples of attention and memory serve to demonstrate the complexity within the terms used to describe cognitive function. To reduce the risk of different processes falling under the same label, the details of the domains being studied, whether attention, memory, executive function, or any other cognitive process, must be clearly operationalized. It is not surprising that studies of cognitive function may find conflicting results in the absence of consistent and clear definitions of the domains under investigation.

As the body of research increases to clarify the understanding of chemotherapy-related changes in cognitive function, it is critical to more fully describe the specific cognitive functions

being assessed and to use or develop instruments that can be used consistently to target those domains to ensure the comparability of studies (or to understand the lack of comparability). An appropriate instrument must be selected that accurately measures the underlying cognitive process of interest. What is clear from evidence to date is that there is a need for the development of instruments that are specific to the issue of chemotherapy-related change in cognitive function, standardization of measurement tools, validation of existing instruments in cancer populations and understanding the sensitivity of instruments in this population.

While Chapter 11 discusses some of the issues related to neurocognitive assessment in much more detail, some of the general issues will be discussed here. To date, there have been approximately 100 different instruments used to assess various domains of cognitive function in cancer research and rarely are these tools used consistently.[9] Extremely few instruments were designed or validated for use in a cancer population. The FACT-Cog is one example of a new tool that has been designed for patient-reported cognitive function, but has yet to be used extensively in this population.[9a] Currently, instruments that were designed for other populations (e.g., dementia) are commonly used. These may not be sensitive enough to detect the subtle changes that are more common during chemotherapy and may only pick up those changes that they were designed to measure. A recent review and meta-analysis[10] provides an overview of a number of instruments available so that investigators may be further informed of the variety of assessment instruments. Although limited to a breast cancer population, this analysis provides an overview of the sensitivity of many of the available measurement tools and is a valuable resource for investigators.

Further complicating the design of research assessing chemotherapy-related cognitive function is the definition of a clinically meaningful impairment. This definition may vary between the instruments and measurement techniques used and may not be comparable between studies or populations. Instead of a predetermined cut-off point, in the absence of consistent measurement methods, research should report the actual measured changes in cognitive function that occur and the patient-reported outcomes of functional abilities. When these details are not provided, the results may be misleading. One study compared assessment criteria in a study of cognitive function among women with breast cancer.[11] When impairment was defined in comparison to published normative data, depending on the cutoff point for "impairment," rates of cognitive impairment ranged from 1% to 37%. This same breast cancer population was then compared to healthy controls and using the same criterion, rates of impairment ranged from 13.7 to 45.4%.[11] Therefore, until there are accepted standards in the field, it is necessary to report not only the details related to measurement, but the frequency and severity of cognitive changes as well. Impairment rates alone are not sufficient.

While designing research studies to examine cognitive function, investigators must also begin to consider the processes and compensation mechanisms of the human brain. This is a broader issue than simply which region of the brain is engaged in activity, but encompasses a longstanding and advancing set of theories and models about cognitive information processing. In the 1960s, Atkinson and Shiffrin proposed a model of memory, which is an information-processing approach to information transfer activities in the brain.[12] This model proposed that there were three distinct stores of memory: sensory memory; working memory (then called short-term memory); and long-term memory. This model suggested there were discrete and sequential steps to memory acquisition and retention. First, all stimuli are detected by the senses and are recorded in sensory memory, where the memory is retained for a very short time period (measured in seconds). Some of these sensory memories are subsequently transferred to working memory so that the information necessary for performing a task is retained. This model proposed that working memory was comprised of only those items that were relevant or necessary for the task at hand. However, not only do sensory memories contribute to working memory, but long-term memories also can be called upon by working memory as needed. There is a bi-directional relationship between working and long-term memory. Some working memories become more permanent memories (long-term memory) and long-term memories are used for active processing of information. At all stages in this model, some memories are lost. This remains a cornerstone of modern theories of memory.

Subsequent information processing models focused on other aspects of memory. For example, Baddeley's Model of Working Memory, developed in the 1970s, proposed three components of working memory that function together and transfer information to and from long-term memory stores.[4,13] According to Baddeley, working memory functions are comprised of the phonological loop, visuo-spatial sketch pad and the central executive. He suggests that these functions have independent capacities, yet to work together to complete tasks. The phonological loop is a limited, short-term storage for sounds. This is not only related to auditory or verbalized sounds, but the 'inner voice' one uses. For example, in counting the number of words in any sentence, it is likely that one uses either an inner voice or counts the words out loud. However, to try to count words speaking (or inner-voicing) the word *the* instead of the number demonstrates the challenges presented when one interferes with the phonological loop.[4]

The visuo-spatial sketch pad is a function that stores visual and spatial information from any stimulus (either verbal or visual). This may involve tasks where one creates a mental image of a scene or of an activity in order to recall it.[4] Similar to the phonological loop, research has shown that when interference prevents one from drawing a mental image in tasks that require it, recall and functional performance decline considerably.

The central executive is proposed to have a key role in working memory in that it serves as a coordinating center for attention, planning and behaviors and interacts with long-term memory. Unlike the phonological loop or the visuo-spatial sketch pad, the central executive is not a storage location, but a management center for activities.[4] In order to perform tasks, the brain calls on central executive resources to coordinate the activities of the phonological loop, visuo-spatial sketch pad and long-term memory. The central executive is also responsible for controlling the flow of irrelevant information (e.g., daydreaming, thinking of what one is going to do later rather than the task at hand) and distinguishes and separates information that is needed from that which can be ignored.[4]

Craik and Byrd proposed a Self-Initiated Processing Theory to address how one may improve working memory when declines occur.[14] They used the information from some of the earlier theoretical models about how working memory functions and proposed the use of environmental supports to replace some of the losses in cognitive resources. For example, research has shown that verbal recall can be significantly improved when simple verbal statements are combined with visual and descriptive text.[14] Additional work has demonstrated that the use of environmental cues can serve as a support for cognitive problems (e.g., placing a medicine bottle near a toothbrush, using blister packed medication indicating the day it is to be taken). Although declines may exist, being aware of the specific areas in which they occur can help develop strategies to compensate for those losses so that functional ability is maintained.

These and many other theories of how the human brain processes information are relevant to the design and interpretation of studies of chemotherapy-related changes in cognitive function. When developing a research protocol that seeks to address any cognitive domain, it is important to refer back to theories related to those cognitive domains so that the context of that cognitive ability can be understood not only for the development of hypotheses and the selection of measurement tools, but importantly, in the interpretation of study findings.

Terminology

The terminology used in the study of cognitive function is important, since the words used by investigators and clinicians communicate a tone and attitude toward the issue. The terms used must accurately reflect the issue and its underlying constructs. Colloquial terms such as chemo brain and chemo fog have been used by some to lighten the discussion, but a decline in one's cognitive abilities is not a joking matter. Declines in cognitive function can severely impact a patient's quality of life, their ability to develop or maintain social support networks, functional performance at work and can negatively impact their ability to perform daily tasks.[15,16] It is important that researchers and clinicians approach this issue utilizing a vocabulary that demonstrates respect for the patient and an objective approach to understanding, resolving and

preventing cognitive problems. Utilizing terminology that makes light of a medical concern undermines the reality of the problem. Changes in cognitive function may or may not include structural changes to the brain, limiting the clinical relevance of the colloquial term "chemo brain." Furthermore, the concept of a "fog" implies a state of confusion or bewilderment (Webster dictionary), when in fact there is a growing body of evidence demonstrating the measurable damage that chemotherapy causes to structures and systems that are intricately involved in cognitive function, none of which are related to the constructs of confusion or bewilderment, but rather with memory, attention and other executive functions needed for higher-order processing.[1] The men, women and children who suffer from these potentially preventable or treatable consequences of chemotherapy deserve no less than the use of accurate terminology from the scientific community.

Definitions for various domains of cognitive function have been published,[9] but these definitions should be placed in the context of the particular study and theoretical approach of the investigators and should be further operationalized based on the measurement tools being used in the study. For example, an operational definition of processing speed may be simply the time needed to complete a task.[9] However, additional details in the terminology used are needed to enable cross-study comparisons. Processing speed may not be equivalent if it is measured using a numeric, verbal, or visual task. These details should be clear both in the research protocol and any publications to avoid the use of broad terms that represent different underlying constructs or processes.

Conceptual Models

The goals of research are to understand, explain, treat or prevent chemotherapy-related changes in cognitive function. As in any research study, it is important to synthesize the assumptions the investigators are seeking to prove in the form of hypothesis statements. Underlying this, however, should be the conceptual framework from which these hypotheses originate. For example, if one hypothesizes that oxidative damage is an important mechanism by which cognitive function is impacted during chemotherapy, that hypothesis must be centered in the broader context of the issue, how it is defined, how oxidative damage may occur, how it might impact cognitive function and how that may lead to reduced functional performance and quality of life. For research to be meaningful in context, it must be grounded in the larger framework of the problem it is designed to address. There are several theories and conceptual models that have been published which may serve as starting points for investigators to use or adapt for their own research protocols. Among these are the Theory of Unpleasant Symptoms (Fig. 1) and the conceptual model of Chemotherapy-Related Change in Cognitive Function (Fig. 2).[9,17]

The Theory of Unpleasant Symptoms is a middle-range theory that is useful for a broad set of adverse effects of chemotherapy treatment. It is relevant for the study of chemotherapy-related changes in cognitive function, in that it takes into account multiple sources (antecedents) of symptom distress, including physiologic (anatomic, genetic, related to the body), psychologic (affective and cognitive variables) and situational (social and physical environment) factors. It also provides the framework for looking at symptoms that do not occur in isolation. Frequently, cancer treatment is associated with a set of symptoms or toxicities, all or some of which may interact with the others.[18] The symptoms experienced by a patient can affect both functional and cognitive performance. One of the features of the Theory of Unpleasant Symptoms is that symptoms are interpreted from the patient perspective and are therefore subjective. Another is the inclusion of specific measurable features of each symptom: intensity (severity), time (duration and frequency of occurrence), distress level (perceived discomfort) and quality (descriptive attributes of the symptom).[17] This general framework can be used to guide the selection of variables to be studied and to identify data collection items in research trials of chemotherapy-related cognitive function.

While middle range theories are too broad to be specifically applied to any one setting, they do encourage thought regarding the rationale for the study, suggest possible relationships

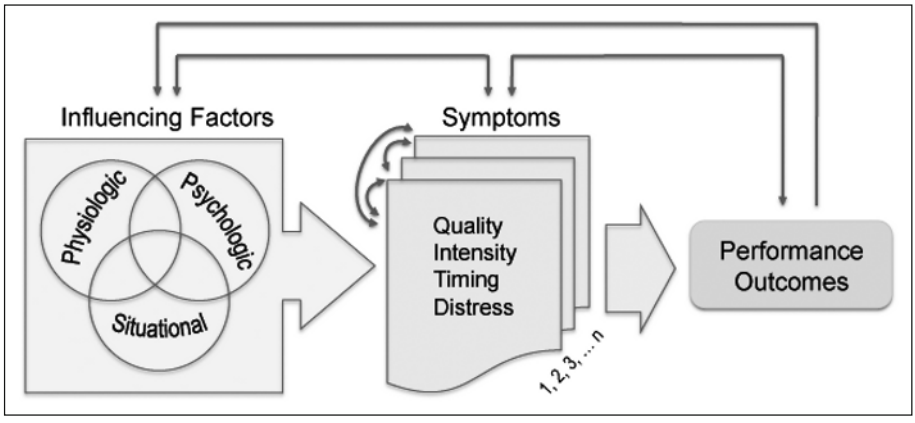

Figure 1. Theory of unpleasant symptoms.

between factors and, most importantly, provide the underlying structure to guide the selection of research aims and study variables.[19] In the study of cognitive function, the Theory of Unpleasant Symptoms may serve as a rough-draft foundation from which any investigator may then develop a more detailed conceptual model for the specific study.

Conceptual frameworks or models, unlike theories, act as general guides for research.[20] The conceptual model of Chemotherapy-Related Change in Cognitive Function has described the phenomenon as follows: "Cognitive function, defined as an individual's higher-order mental processes, may be altered among individuals diagnosed with cancer along two distinct and interacting pathways: a) cancer diagnosis (the meaning of cancer), leading to anxiety, stress, distress and depression; and (b) direct physiologic effects of cancer treatment, both of which may affect cognitive function."[9] While this descriptive-relational statement may or may not apply to any single investigator's point of view on the issue, it does describe the type of detail needed at the conceptual level for direct application to a research setting. This conceptual model, however, is not sufficient in and of itself, but rather is the background from which proposed hypotheses within any research project are developed. The use of conceptual models

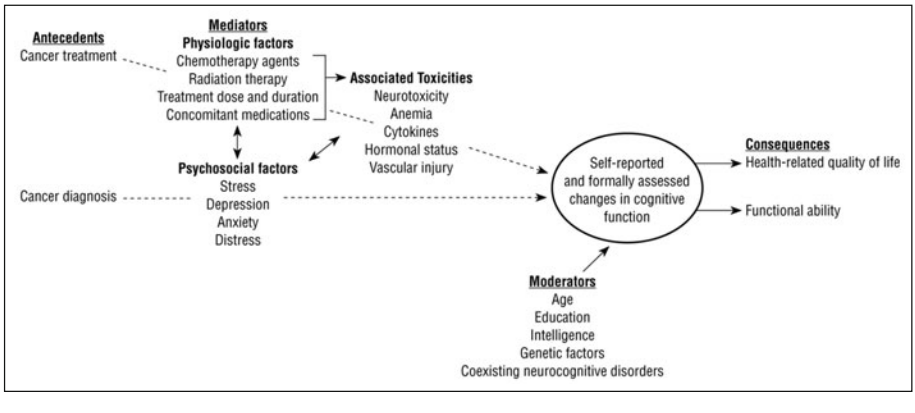

Figure 2. Conceptual model of chemotherapy-related change in cognitive function. Reprinted with permission from Hess LM, Insel KC. Chemotherapy-Related Change in Cognitive Function: A Conceptual Model. Oncol Nurs Forum 2007; 34(5):991. Copyright 2007 by the Oncology Nursing Society.[9]

can orient the research to select variables of interest, as well as provide a description of the setting in which the research can be implemented. Each investigator should start at the broad, conceptual model level of an understanding of the issue under investigation prior to developing a research protocol.

The conceptual model of Chemotherapy-Related Changes in Cognitive Function was developed from a systematic review of the literature, which was used to identify the scope of cognitive function research trials conducted through 2006. The evidence was synthesized into themes under the broad headings of conceptual definitions, antecedents (preconditions or preceding events), moderators (factors that influence the strength and direction of relationship between independent and dependent variables), mediators (mechanisms of action) and consequences (outcomes of interest). In this model, the antecedents are the cancer diagnosis (physiological impact of disease) and the meaning of cancer (the psychosocial impact of disease). For a condition to be considered chemotherapy-related cognitive function, the model narrowed the population to those receiving chemotherapy for cancer and suggested that two distinct, yet interacting, factors were involved in changes in cognitive function. The moderators (those factors that impact the strength or direction of the relationship between chemotherapy and cognitive function) were identified from the literature and included age, education, general intelligence, genetic factors and any other cognitive problems. These factors may play a role in the cognitive declines experienced during chemotherapy and are some of the factors that should be controlled for in research. Mediators, on the other hand, are those factors that explain how the decline occurs (e.g., mechanisms of action). Less is known about the specific biological changes that lead to declines in cognitive function among individuals being treated for cancer, but a number of possible mechanisms are described in more detail in Chapter 13 of this book. Chemotherapy treatment may act on the body by causing oxidative damage, hormonal changes, or vascular damage, for example, and may lead to a host of toxicities that may impact cognitive function as well (e.g., anemia, nutritional deficiency). Much more work is needed in this area. It is critical that studies designed to prevent or treat changes in cognitive function utilize agents or interventions that may directly impact the proposed mechanism of action. Any intervention study must include a clear rationale for the selection of that intervention and how it might impact or compensate for the ways in which chemotherapy led to cognitive decline. Intervention studies are described in more detail later in this chapter. The consequences of changes in cognitive function are the things that matter to patients in their daily life, such as quality of life and functional ability. Research should take not only the measurable changes in cognitive function into account, but should also examine the impact of these declines on patient-reported and clinical outcomes.

While this is only one example of a conceptual model specific to the role of chemotherapy in cognitive decline, investigators designing a research trial should clearly present a conceptual model for their own approach to the issue. It is important to note that all conceptual models are dynamic. As knowledge is gained in this field, there is a need to constantly revisit conceptual models and frameworks and to adapt them to new information.

Designing Research Trials

As discussed in the first part of this chapter, prior to developing specific aims for a research study, investigators should have developed a conceptual model or framework as the foundation from which the research trial will be developed. The conceptual model, at a minimum, should describe the antecedents, moderators, mediators, consequences and relationships between these factors. This orients the researcher to the broader scope of the issue. Following development of the proposed conceptual framework, hypotheses and specific aims can be developed that will study certain aspects of the model. This model or framework should be the basis of the study protocol (research plan). The U.S. National Institutes of Health provides a number of clinical trial protocol templates on their various center websites for reference. Sample templates are available at both the National Cancer Institute's (NCI) Division of Cancer Prevention Protocol

Development Office (http://prevention.cancer.gov) and Cancer Therapy and Evaluation Program (http://ctep.cancer.gov) websites. These guides are also useful for studies outside of the NCI review system, as they provide instruction as to key considerations about the quality of research that should be conducted regardless of funding source. In general, Table 1 presents the range of items that should be considered for inclusion in a research protocol to study chemotherapy-related changes in cognitive function.

Table 1. Items to be addressed in a research protocol document (adapted from templates at www.nhlbi.nih.gov and www.cancer.gov)

Main Sections of Protocol Document	Items To Be Included
Introduction	Abstract of the study
	Primary hypothesis
	Study purpose
Background and Rationale	Prior studies and literature review
	Conceptual framework
	Rationale for current study
Objectives	Primary aim(s)
	Secondary aim(s)
	Exploratory aim(s)
	Outcome measures to be assessed (for each aim)
	Rationale for outcome measures (for each aim)
Intervention to be used	Preclinical data (if intervention is an agent)
	Theoretical data (if intervention is behavioral)
	Clinical data to date
	Rationale for selection of intervention strategy (proposed mechanisms of action)
	Risk/benefit of dose (agent) or of activities (behavioral)
Study design	Summary of design
	Participant inclusion and exclusion criteria
	Inclusion of women and minorities
	Ethical considerations
	Participant recruitment and consent process
	Randomization methods and blinding of treatment arm
	Treatment regimen, including run-in if applicable
	Participant retention plan
	Data collection and follow-up
	Data collection and follow-up in cases of early withdrawal

continued on next page

Table 1. Continued

Main Sections of Protocol Document	Items To Be Included
Intervention	Description of agent or intervention
	Reported adverse events and potential risks
	Agent distribution and availability
	Preparation and administration
	Contraindications, concomitant medications
	Dose modification
	Adherence monitoring
	Packaging, receiving, storage, dispensing and return/ destruction (agent studies)
Study procedures	Screening for eligibility
	Scales/instruments used to assess outcomes (sensitivity, validity and reliability in target population)
	Schedule of assessments and events
	Baseline or prestudy procedures/assessment
	Schedule of each study visit, procedures/assessments
	Procedures/assessments at study completion
	Post-intervention follow-up period (procedures/assessments)
	Methods for clinical procedures
Statistical Plan	Criteria for evaluation and endpoint definition
	Primary endpoint
	Secondary endpoint
	Other endpoints
	Randomization/stratification procedures
	Criteria for participant withdrawal
	Criteria for study termination
	Sample size justification and power
	Planned statistical analyses
	Evaluation of toxicity
	Reporting and exclusions
	Attrition rate/missing data
	Accrual rate
	Interim analysis
	Ancillary or correlative studies
Data management plan	Case report forms
	Source documents

continued on next page

Table 1. Continued

Main Sections of Protocol Document	Items To Be Included
	Record storage and shipment
	Record retention
	Data entry plans and procedures
	Quality assurance/quality control plan
Safety monitoring plan	Data and Safety Monitoring Board role
	Plan for collection and reporting of adverse events
	Duration of collection and reporting of adverse events (poststudy assessments)
Specimen management	Laboratories
	Collection and handling procedures
	Shipping instructions
	Tissue banking
Appendices	Forms and questionnaires
	Informed consent

Study Design

First, one must assess the conceptual model and the questions that one wishes to answer in the research trial. While no single protocol can address every aspect of any complete conceptual model, this information guides the design of the trial and places the study in the context of the larger issue. The questions (study aims) may need to be narrowed so that the study is adequately designed and has sufficient statistical power to answer the primary aims. Secondary and exploratory aims may be included for items that are of interest but that may not be of sufficient interest to warrant an increased sample size, or if the sample size necessary for all aims is not feasible. It must be stated that any aims without sufficient power (e.g., less than 80%) may result in a Type II error (false negative findings). Secondary and exploratory aims can never be interpreted as definitive evidence, even if conducted in the context of a randomized clinical trial.

The study design to be used in the evaluation of chemotherapy-related change in cognitive function is an important consideration that will impact decisions to be made when developing the protocol and intervention and to determine what will be learned from the study. Traditionally, levels of evidence summarize how strong the results of the study may be in terms of understanding the issue. High quality studies (Grade A/Level I) are those that by design are less likely to present biased findings and should be taken into consideration with regard to the decision to implement the findings into future research or clinical practice. Studies of lower grades (B and below) are considered to be fair to weak evidence and are more likely to contain bias that limits the validity and reliability of findings.[21] Table 2 presents the strength of evidence for the design of trials that may seek to treat or diagnose chemotherapy-related changes in cognitive function. Based on the Oxford Criteria for levels of evidence, Grade A evidence is limited to level 1 studies; Grade B evidence is level 2 or 3 studies, or extrapolations from level 1 studies; Grade C evidence is level 4 studies, or extrapolations from level 2 or 3 studies; and Grade D evidence is level 5 or inconsistent or inconclusive studies at any level.[22]

When designing a research study, one should always strive to produce the highest level of evidence possible within the resources available and the current state of knowledge. Certainly in the absence of any preclinical or theoretical data, conducting a randomized intervention trial to attempt to reduce the impact of chemotherapy on cognitive function is not appropriate. Once the

Table 2. Evidence-based medicine, levels of evidence, adapted from Phillips et al[22]

Level of Evidence	Treatment/Prevention Studies	Diagnosis Studies	Differential Diagnosis/Symptom Prevalence Studies
1a	Systematic review of randomized controlled trials (RCTs) (with homogeneity)	Systematic review (with homogeneity) of Level 1 diagnostic studies; clinical decision rule with 1b studies from different clinical centers	Systematic review (with homogeneity) of prospective cohort studies
1b	Individual RCT (with narrow confidence interval)	Cohort study validating the findings of prior evidence with good reference standards (independent of the test, applied blindly or objectively to all patients); or clinical decision rule tested within one clinical center	Prospective cohort study with good follow-up (more than 80% complete and adequate time for diagnosis to emerge)
1c	All or none RCTs (all patients experienced cognitive impairment before the treatment became available, but some now do not while on it; or when some patients experienced cognitive impairment before the treatment became available, but none do now)	A diagnostic finding whose specificity is so high that a positive result rules-in the diagnosis or a diagnostic finding whose sensitivity is so high that a negative result rules-out the diagnosis	All or none case-series
2a	Systematic review (with homogeneity) of cohort studies. Worrisome heterogeneity is 2a-	Systematic review (with homogeneity) of Level >2 diagnostic studies. Worrisome heterogeneity is 2a-	Systematic review (with homogeneity) of 2b and better studies. Worrisome heterogeneity is 2a-
2b	Individual cohort study or low quality RCT (<80% follow-up or wide confidence intervals)	Exploratory cohort study (e.g., collects information and trawls the data such as by a regression analysis to find which factors are 'significant') with good reference standards (independent of the test and applied blindly or objectively to all patients); clinical decision rule after derivation, or validated only on split-sample or databases	Retrospective cohort study, or poor follow-up (e.g., <80% or not sufficient time to detect diagnosis)

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Table 2. Continued

Level of Evidence	Treatment/Prevention Studies	Diagnosis Studies	Differential Diagnosis/Symptom Prevalence Studies
2c	"Outcomes" Research; Ecological studies		Ecological studies
3a	Systematic review (with homogeneity) of case-control studies	Systematic review (with homogeneity) of 3b and better studies. Worrisome heterogeneity is 3a-	Systematic review (with homogeneity) of 3b and better studies. Worrisome heterogeneity is 3a-
3b	Individual case-control study	Nonconsecutive study; or without consistently applied reference standards	Nonconsecutive cohort study, or very limited population
4	Case-series, poor quality cohort studies, or poor quality case-control studies. Poor quality means there were no clearly defined comparison groups and/or failed to measure outcomes in the same, objective way in both exposed and non-exposed individuals or cases and controls (e.g., blinded) and/or failed to identify or appropriately control known confounders. For cohort studies, poor quality studies may have failed to carry out a sufficiently long and complete follow-up of patients.	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

health issue has been identified and described, as is the case with cognitive function studies in breast cancer, research should focus on the basic sciences. In biological systems, this refers to the inter- and intracellular mechanisms of disease. In behavioral systems, basic science refers to basic psychosocial processes. As with any health issue, but particularly with the effects of chemotherapy on cognitive function, both biological and behavioral systems must be considered. This can be evaluated in a stand-alone study, or integrated into observational or interventional trials. Correlative studies are integrated into a larger trial and are designed to test the relationship between the condition and the causative factors and may be either exploratory or definitive.[23] The National Cancer Institute has provided examples of correlative studies and these may be applied to specimens collected in research studies of cognitive function, such as: phenotypic or genotypic alterations which appear to correlate with the development of cognitive impairment; studies of chromosomal rearrangements or deletions that may be used for risk assessment or prognosis; or characterization of immune response in relation to cognitive functional abilities.[24] Ancillary studies are those designed to test hypotheses related to, but not part of the original study aims. While correlative studies may be imbedded within a study protocol, ancillary studies are "add-on" studies that are not part of the original study aims or design.[25] The collection of samples (tumor or serum banking) within a research protocol provides a resource for future ancillary studies.

Experimental and Non-Experimental Designs

The research study should be designed in such a way as to control variance as much as possible so that the outcome of interest can be examined with minimal confounding. A well-written, thorough protocol document is one method to reduce variance, but the control of extraneous variables can be problematic depending on the study design, eligibility criteria and heterogeneity of the study population. There are tradeoffs that must be made during the planning stages of a research study. By limiting the study to a very homogenous population, many extraneous variables can be controlled or removed from the study. However, the results will not be generalizable to a larger population. The use of experimental designs (e.g., randomization) is another way to control these extraneous variables, by ensuring that the factors that could influence outcomes are distributed equally between the treatment and control groups. When experimental designs are not possible, the investigator may simply choose to build those variables into the analysis plan to explore their interaction with the outcomes of interest.[26] The use of a comprehensive conceptual model can help investigators identify and address potential sources of confounding. Some of the study designs relevant to the evaluation of chemotherapy-related changes in cognitive function are briefly described below, including several limitations.

Prevalence and incidence studies contribute to the knowledge of chemotherapy-related changes in cognitive function by defining the extent of the problem and so that intervention studies can be adequately powered. Incidence studies must be longitudinal, since these studies track the number of new cases over a given time period. For example, if a population of cancer patients is enrolled prior to chemotherapy and their cognitive function is assessed periodically throughout treatment, this study could assess the incidence of declines during chemotherapy for that population. Prevalence studies may be cross-sectional, since they identify the number of individuals who experience the problem at or during any specified time period. For example, if any group of individuals being treated for cancer were assessed at only one time point (e.g., following completion of treatment), one could estimate the prevalence of the issue at completion of therapy for that sample. The prevalence rate is calculated as the number of individuals exhibiting decline, divided by the total number of persons in that study population at that time. However, in the absence of population-based screening, incidence and prevalence rate estimates can only be directly related to the enrolled study population. Generalizability is limited by the size and heterogeneity of the sample population, but is further impacted by the variability in measurement and the definitions of impairment used in the field of cognitive function and cancer.[11] Prevalence estimates for chemotherapy-related changes in cognitive function been reported to range widely, from 17% to 75% across studies.[27]

Cohort studies follow a group of individuals selected on specific eligibility criteria, usually due to the risk or a diagnosis of a health condition.[28] Cohort studies are generally observational and may be conducted prospectively (following a group of participants over time), retrospectively (examining the past exposures or events of a group exhibiting the outcome of interest), or may include a combination of retrospective and prospective methods. Cohort studies are useful in exploring the incidence of an event (prospective cohort studies) or the possible attributable risk of past exposures. One limitation of cohort studies is the lack of an external comparison group, although the cohort may include internal controls (e.g., some of the cohort may experience declines in cognitive function, while others may not).

Case-control studies include a comparison (control) group. Ideally, the control group selected should be identical to the cases on all factors, with the exception of the "case" status. Eligible participants for a case-control study could include individuals with cancer who are the same on all factors considered relevant (diagnosis, age, gender, education, chemotherapy, etc), but differ in that the cases experienced cognitive decline and the controls did not. Research could then be completed to compare the groups to find out what may have differed and what may be associated with the cognitive decline. Cases could also be cancer patients, while controls may be otherwise healthy individuals whose cognitive function is compared at one time point (cross-sectional study) or prospectively. Similar to the case-control design, *non-equivalent group studies* assign the experimental and control groups on any factor of interest (e.g., chemotherapy versus no chemotherapy). Case-control and non-equivalent group designs may be used for observational or intervention studies. Of particular relevance to this field, it is not ethical to randomize cancer patients to chemotherapy versus no chemotherapy to assess the impact of treatment on cognitive function and quasi-experimental designs are needed. A non-equivalent group design was used to enroll women who had been diagnosed with postmenopausal breast cancer into a research trial. These women had already decided that they were either going to receive chemotherapy or hormonal medications.[29] In this study, women underwent neurocognitive assessment prior to initiating treatment, following completion of treatment and one year after completion of therapy. This study found that women receiving chemotherapy were more likely to experience cognitive decline at the posttreatment assessment time point, but at one-year follow-up, these changes were equivalent between groups. One explanation suggested that hormonal therapy may also be a factor related to changes in cognitive function.[29] It is important to fully collect and describe factors that differ between groups, especially those that may contribute to differences in cognitive function in case-control, non-equivalent group and any other nonrandomized (quasi-experimental or non-experimental) or randomized multiple group design. Groups may differ on other important factors that may contribute to differences and these factors should be accounted for in the analysis. Selection bias is a concern for both case-control and cohort study designs.

Randomized trials are considered the gold standard and are an example of an experimental design. While it is unethical to expect that patients will be randomized to chemotherapy versus no chemotherapy to assess treatment as a causal factor in cognitive decline, it is possible to randomly assign individuals to a treatment or preventive strategy versus a control or observation only. While there remains a lack of knowledge about the mechanisms of cognitive decline, this knowledge will contribute to the ability to conduct well-designed, adequately powered and theoretically/mechanistically-based randomized intervention trials. Studies of cognitive function have been linked to randomized chemotherapy trials as either secondary aims, or as ancillary studies. Including cognitive function endpoints within a larger clinical trial can help to identify the impact of specific treatment regimens on cognitive outcomes, while controlling for other potential confounders via the randomization process. In 1998, cognitive function was assessed at one time point between 1.5 and 2.4 years after therapy among three groups of women who were enrolled in clinical trials in the Netherlands Cancer Institute.[30] Study participants were women with breast cancer who were randomized to receive either high-dose or standard-dose chemotherapy as part of the clinical trial, or who did not receive chemotherapy (controls who were not part of the randomized trial). Comparisons between the high-dose chemotherapy group and control group demonstrated an

increased risk of cognitive impairment associated with chemotherapy (odds ratio (OR) = 8.2; 95% confidence interval (CI), 1.8-37.7; $P = 0.006$). There was no significant difference in cognitive impairment between the high-dose and standard-dose chemotherapy groups (OR = 3.5, 95% CI, 1.0-12.8, $P = 0.056$) or the standard-dose and control groups (OR = 2.4, 95% CI, 0.5-11.5, $P = 0.287$).[30] Unfortunately, this study did not find significant differences between the groups that were balanced by randomization, but was among the first to suggest there may be a relationship between chemotherapy dose intensity and cognitive outcomes.[30]

In addition to unexplained variance, all experimental (randomized trials), non-experimental (single group trials) and quasi-experimental (multiple group, nonrandomized trials) designs are at risk of loss to follow-up. This is particularly a problem when one group of individuals is more likely to discontinue the study than others, as the results of the study will be biased. Single-group studies are further at particular risk of history and maturation effects.[31] Some events may be more likely to occur over time (e.g., as external events influence test results—history effect, or as the population ages—a maturation effect). In test-retest designs, individuals may learn from the first experience with the assessment test and simply due to that fact, perform better on the second assessment. If the study protocol is not sufficiently explicit, or if multiple test administrators conduct the assessments, bias may be introduced that affect the study results purely due to the process by which the study procedures were implemented. While every form of bias cannot be controlled, a carefully designed protocol that takes these and other potential bias and threats to validity into account will reduce this risk. While all potential threats to bias and internal or external validity are beyond the scope of this chapter, details are available elsewhere.[31,32] Investigators should consider and address all potential sources of bias to the extent possible in the design of a research protocol.

Phases of Research

When designing a clinical trial of an agent that may require U.S. Food and Drug Administration (FDA) approval, there are a series of phases of research that must be conducted. In the design of trials of behavioral strategies or nutritional supplements, which are not regulated by the FDA, investigators may take a more flexible approach to developing and testing intervention strategies, but regardless of the regulatory requirements, there must be sufficient evidence for both safety and efficacy (based on basic science, preclinical and/or early phase research) and hypothesized mechanisms of action prior to conducting a trial of any behavioral or biomedical intervention.

Pilot studies are useful to conduct prior to implementation of a larger trial. These studies, however, are not designed to produce meaningful scientific knowledge. The goal of conducting pilot research is to test the feasibility and acceptability of a proposed research plan, or to explore the assessment of outcomes prior to the development and implementation of a larger study. This is important in the interpretation of pilot study data, in that pilot research is neither powered for nor designed to provide results in the data. Several important reasons have been proposed in support of conducting pilot research prior to the implementation of clinical trials. These include: developing and testing adequacy of research instruments; assessing the feasibility of a study or survey; determining if a research protocol is realistic; determining the potential time frame; testing recruitment and retention strategies; identifying logistical issues; estimating variability for future sample size determinations; identifying potential problems in the study design; preliminary data collection; training staff in the processes and procedures of study implementation; and identifying resource needs for the subsequent study.[33] A pilot study was conducted to evaluate the feasibility and to obtain preliminary estimates of the ability to detect declines using a web-based assessment of cognitive function among women being treated for ovarian cancer.[34] This study identified several logistical challenges, such as the use of traveling nursing staff, which were addressed prior to implementing a larger study through the Gynecologic Oncology Group (GOG) (GOG Protocol 0256). This study also determined aspects of the study implementation that needed to be addressed in the study protocol (e.g., computer access points and training requirements). This likely avoided many more costly mistakes that could have impacted the quality of study data for the larger trial.

In addition, the pilot study was able to successfully implement the computer test, which was able to detect cognitive declines in the majority of participants, suggesting there may be evidence of the acceptability and sensitivity of the instrument in the target population.[34] Pilot studies are important and necessary steps in the design of a research project, but are limited in that the data produced cannot be as definitive evidence for the phenomenon under study.

Research trials are categorized into four phases. *Phase I* research is designed to test the safety of an intervention in a relatively small group of participants (usually less than 50). *Phase II* research may either be a single-group study (Phase IIa) or a randomized study (Phase IIb) and usually include slightly more participants than Phase I trials (approximately 100). At this stage of research, investigators are seeking to explore the potential efficacy of an intervention. Efficacy is not measured in terms of the final outcome of interest, but Phase II trials often test surrogate biomarkers (intermediate endpoints) that have been shown to reflect future outcomes.[35] While Phase I trials can usually be completed within weeks, Phase II trials often last several months, or until the intermediate outcome can be measured. Once there is evidence of the feasibility of a research study (pilot study), early phase evidence of the safety and acceptability of the intervention (Phase I) and potential efficacy (Phase II), the intervention may then go on to be tested in a *Phase III* trial. Phase III trials are larger randomized trials that can last from months to years, depending on the outcome of interest. Similar to Phase II research, Phase III trials must include power calculations and have a sample size sufficient to detect the outcomes of interest. Whereas treatment Phase III trials can easily require many hundreds to thousands of participants, prevention Phase III trials may require thousands to hundreds of thousands of individuals.[35] Consider the case of chemotherapy-related change in cognitive function. To test a preventive strategy that may have a 30% effectiveness rate, one must also factor in that only a subset of the cancer population may be expected to experience cognitive decline. Hypothetically, if only 50% of a population is expected to experience the decline during the time period of the clinical study, one must account for that in the power analysis. In essence, instead of seeing 30% of the sample respond, only 30% of the 50% might respond (15%, requiring perhaps about 1000 patients per group). With treatment research, a study would only enroll individuals experiencing the phenomenon, so a 30% effectiveness rate can be calculated based on all enrolling participants, rather than only a subset (perhaps requiring a sample size of 500 patients, or 250 per group, for an intervention with the same expected efficacy). Further complicating prevention research, attrition is more likely when participants are not being treated for a concern that currently affects them. More attention must be given to providing incentives throughout the study and a clear plan for retention strategies must be in place to reduce attrition in prevention trials. In either case, anticipated attrition rates must be included in the power calculations. For prevention research to be most effective and to reduce the participants necessary to detect statistically significant results, investigators may wish to limit enrollment to those at highest risk of experiencing the event. At this point in time related to chemotherapy-related changes in cognitive function, there is not sufficient information to clearly identify those individuals at highest risk of cognitive decline. This is an important area of research needed for the design of effective preventive strategies. Some studies have incorporated cognitive assessments into trials that randomize participants to two different treatment groups.[36] Unfortunately, since these studies are powered on the clinical outcomes of interest (e.g., tumor response/survival), it is unlikely that investigators will wish to address sample size issues to consider the cognitive outcomes for secondary endpoints, particularly in the absence of supplemental funding and there will remain a substantial risk of false negative results. While Phase III studies test efficacy (e.g., can the intervention work), *Phase IV* trials are effectiveness studies, designed to understand if an intervention or treatment will work in non-experimental settings. These are surveillance or postmarketing studies that are conducted to assess the reliability of clinical trial findings (e.g., long-term safety and efficacy), to evaluate patient quality of life, to compare similar products, or sometimes to conduct cost-effectiveness analyses.[35]

Outcomes Assessment

When designing a clinical trial or research study investigating cognitive function, it is important to clearly define which outcomes will be measured and how they will be measured. As stated earlier, measurement issues are described in more detail in Chapter 11. However, when selecting an instrument to assess cognitive function, one must reflect back to the conceptual framework underlying the study and recall that cognitive function is a very global term that encompasses a host of higher-level processing skills. Cognitive outcomes can be measured clinically (computerized, response-based or pen-and-paper assessments) or can be patient-reported (the patient's perceptions on their own functioning). Further, changes in quality of life may be a further outcome of cognitive function decline as well. It is important to conceptualize in the study design what outcomes are of interest and how they will be assessed, taking the sensitivity and validity/reliability of the measurement tool into consideration. As described earlier, attention, memory, recall and other domains and specific processes within the broad scope of cognitive function cannot be directly compared. Each cognitive domain and process is a unique, but related, set of cognitive processes. When assessing cognitive function in research protocols, keep in mind that the underlying constructs related to cognitive function are being measured. The underlying construct is defined by how it is measured.

Conclusion

Regardless of the phase of research or of the experimental design, a conceptual model-based approach to the design and implementation of research can strengthen not only the design and the findings, but can enhance the ability to understand and interpret the findings in the context of the larger body of scientific evidence. This is especially important in studies of chemotherapy-related changes in cognitive function where a complex approach, involving both biological and psychosocial issues, is needed.

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Chapter 9

Neuropsychologic Testing for Chemotherapy-Related Cognitive Impairment

Jamie S. Myers*

Abstract

No standard has been established for neuropsychologic testing to identify and quantify chemotherapy-related cognitive impairment (CRCI). A number of issues exist related to the complexity of the phenomenon and lack of correlation between standardized objective tests and subjective tests by patient self-report. Review of the issues related to current neuropsychologic tests used to evaluate CRCI provides support for qualitative examination of patients' lived experience in order to guide the development of more accurate tests.

Introduction

Chemotherapy-related cognitive impairment (CRCI) is now recognized as a serious potential sequela to treatment. Estimates of frequency range from 75-95% in patients evaluated shortly following the completion of treatment and 17-35% in patients evaluated two or more years after therapy.[1] No standard has been established for the use of neuropsychologic tests to identify and quantify CRCI[2] and a number of issues exist related to the complexity of the phenomenon and lack of correlation between standardized objective tests and subjective tests by patient self-report.[3,4] The purpose of this paper is to review the neuropsychologic tests most commonly used to assess CRCI and outline current issues and concerns.

Neuropsychologic Test Overview

Standardized neuropsychologic tests have been developed to evaluate cognitive performance across a number of domains such as attention and concentration, executive function, information-processing speed, language, motor function, visuospatial skill, learning and memory (see Table 1).[5] Learning and memory sometimes is divided into visual and verbal memory (Nail, 2006). Abstract reasoning also is periodically assessed as a component of neuropsychologic testing.[6] Special training is necessary to administer and score these tests. Selection of appropriate tests to evaluate specific phenomenon is typically done by neuropsychologists as is the training and oversight of staff administering the tests and the interpretation of test results.[6] Results provide insight into specific areas of brain injury based on individuals' performance on tests designed to elicit objective data related to the specific cognitive domains (see Table 1).[7]

Numerous tests exist for each of the domains of cognitive function. A review of the literature related to neuropsychologic testing for CRCI provided information in support of the fact that there is lack of standardization and consistency related to testing for CRCI. A summary of this

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Table 1. Domains of cognitive function: corresponding components and brain anatomy[5-7,9]

Domain	Definition	Components	Associated Anatomy
Attention and Concentration	Enable ability to triage relevant inputs, thoughts and actions while ignoring those that distract or are irrelevant. Ability to focus and sustain attention.	Arousal Selective attention Sustained attention or vigilance Directed attention	Ascending reticular activating system Frontal subcortical network Rt hemispheric prefrontal and parietal regions Prefrontal cortex (cingulated cortex, amydgala)
Executive Function	Higher order cognitive Processes that include Initiation, planning, hypotheses generation, cognitive flexibility, decision making, self-regulation, judgment, feedback utilization and self-perception.	Initiation Planning Cognitive flexibility Self-monitoring Self-regulation	Anterior cingulated cortex Dorsolateral prefrontal cortex
Information-Processing speed	Ability to rapidly process simple and complex information. Linked to all other cognitive domains due to tactile, auditory, verbal and visual nature of input.		Parietal and frontal lobes
Language	Ability to comprehend and communicate written and spoken symbolic information	Verbal or written expression Reception Repetition	Supplementary, motor, prefrontal cortices Wernicke's area Broca's area

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Table 1. Continued

Domain	Definition	Components	Associated Anatomy
Motor function	Performance related to speed, strength and coordination.	Speed Strength Coordination Dexterity Apraxia	Frontal lobe (premotor and primary motor areas), parital lobe (somatosensory areas), cerebellum, brain stem.
Visuospatial skill	Ability to process and interpret visual information regarding where things are situated in space.	Perception Construction	Primary visual cortex in posterior occipital lobe, temporal lobes, parietal lobes
Learning and Memory	Ability to acquire, store and access new information	Learning Short-term memory	Reticular activating system, dorsolateral prefrontal cortex, parietal cortex, medial temporal lobe, amygdale, orbitofrontal cortex
		Long-term memory	Frontal and anterior temporal lobes
		Recall	Prefrontal cortex
		Recognition	
		Verbal memory	Left hemisphere
		Visual memory	Right hemisphere

chapter is provided in Table 2. Information in the table includes a breakdown of the variety of tests used within each of the domains as well as an indication of the overlap for many of the tests across multiple domains. References are cited for the studies in which the tests were used to measure CRCI. A description of the testing procedures is provided. The number of neuropsychologic tests used in the studies reviewed ranged from as few as three[8] to as many as 32.[6] Considerable overlap was noted across the domains.

Jansen et al[9] conducted a meta-analysis of the various neuropsychological tests used to detect CRCI in patients with breast cancer. They reviewed 13 studies and utilized meta-analysis software to calculate standardized mean difference effect size and a 95% confidence interval. Effect sizes were interpreted as negligible (<0.20), small (0.20-0.50), medium (0.50-0.80) and large (greater than 0.80). Tests that were used in at least two or more studies were included in the analysis and 30 tests were examined. Only 6 of the tests were sensitive to CRCI in 4 of the 8 cognitive domains (language, motor function, visuospatial skill and verbal memory) (see Table 3). The authors noted that "most of the neuropsychological tests used in the studies performed to date do not appear to be sensitive enough to detect changes in cognitive function" (p. 1004).

The High Sensitivity Cognitive Screen (HSCS) has been selected for testing CRCI due to sensitivity for detecting subtle cognitive impairment and the fact that this battery of tests only takes 25-30 minutes to administer.[10,11] The HSCS has been validated for individuals aged 16-65 and classifies cognitive performance as normal, borderline, or abnormal. The degree of abnormality is ranked as mild, moderate, or severe. The HSCS can be used to measure performance on memory, language, visual-motor, spatial, attention and concentration and executive function domains.[10] Good test-retest (0.70-0.80) and inter-rater reliability (0.98) has been demonstrated for the HSCS.[12] The HSCS has been compared to more comprehensive neuropsychological tests and was seen to correctly classify 93% of subjects across the normal versus abnormal dichotomy.[11]

The HSCS has not proven sensitive across all studies for CRCI. No significant differences were seen for women with breast cancer who were tested at baseline, prior to 3rd cycle of chemotherapy and following completion of therapy although the women perceived significant impairment in cognitive function.[13] The HSCS was also used in 3 studies by Tchen et al[11] in which differences in cognitive function were demonstrated between women receiving chemotherapy for breast cancer and healthy controls. Vardy et al[12] noted that the HSCS should not be used for studies involving repeated measures separated by short intervals due to practice effects.

The lack of consistency across studies for the HSCS is but one example of some of the challenges experienced by researchers attempting to objectively assess patients for the presence and severity of CRCI. A more detailed discussion of current issues follows.

Issues Related to Neurocognitive Testing for CRCI

A number of challenges exist related to the use of neuropsychologic tests to evaluate the incidence and type of cognitive changes patients experience as a result of receiving chemotherapy. Many of the early studies were retrospective in nature, thus no comparisons were able to be drawn related to baseline cognitive function. The mixed results seen in these early retrospective trials were further complicated by a lack of consistency in the tests selected for each study as well as overlap between tests selected to evaluate specific cognitive domains.[2,9] The need for prospective trials has been acknowledged, however the lack of consensus regarding a standard neuropsychologic battery for CRCI remains.[14]

Results from several studies indicate that standard neuropsychologic tests may not be sensitive enough to objectively quantify the subtlety of CRCI.[8,9,15,16] One concern is the lack of ecological validity of available tests to simulate real-life challenges related to multi-tasking, distractions and the need for sustained attention compared to the laboratory setting.[17-20] Lack of correlation has been demonstrated between patients' self-report of their perceptions of cognitive changes from baseline and performance on standard neuropsychologic tests (Schagen, et al, 1999). Many participants have been shown to have very high levels of baseline performance. Although more effort may be required to perform the tasks associated with testing, performance still falls within the

Table 2. Neuropsychological tests used to study CRCI

Type of Test	Test Name	Citations	Description	Domain Overlap
Attention and Concentration	PASAT	6,18	Rapid random series of digits are presented (1 number every 2 seconds). Patient is required to add consecutive pairs of numbers. Scores are derived from the total number of correct additions in one series of 51 digits (max score = 50) and compared with published norms. Significant practice effect is seen from 1st to 2nd presentation. Assesses focused attention as well as rapid new problem solving.	Processing speed and vigilance
	HSCS	11,12,25,26	Paper and pencil test designed to detect subtle changes in cognitive function. Can be administered in 25 minutes. Provides a discrete classification of overall cognitive function (normal, borderline; mild, moderate, severe) and assesses 6 areas of performance. Includes tests for sentence and word-pair repetition, reading and writing from dictation, shape rotation and completion, conflicting stimuli and sentence construction.	Verbal memory, language, visuomotor, visuospatial, executive function
	CogHealth	12	Brief computer test that requires 18 minutes to complete; No previous keyboard skill required. Minimal practice effects even at short intervals of administration. Includes 8 tasks to evaluate reaction time, decision-making, working memory, executive function, continuous performance matching and new learning. Validated against a number of other tests (correlation 0.23-0.86). Intra-class correlations on retesting range from 0.69-0.90.	Memory, executive function, learning
	Headminder	27,28	Computerized test with multiple forms of most subtests. Validation demonstrated against numerous traditional neuropsychological tests with correlation on strongest factors ranging from 0.31-0.74. Test-retest reliability between 1st and 2nd assessment ranging from 0.68-0.80. Administration time is 30 minutes.	Reaction time, processing speed, memory, executive functioning
	Trail-making test A and B	6,8,11,29-31	Timed 2 part test in which one must draw lines to connect consecutively numbered circles on one work sheet (part A) and then connect the same number of consecutively numbered and lettered circles on another work sheet by alternating between consecutive letters and numbers (part b).	Visual conceptual and visuomotor tracking, psychomotor speed, multitasking

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Table 2. Continued

Type of Test	Test Name	Citations	Description	Domain Overlap
Attention and Concentration (continued)	Stroop Test	6	Patient must substitute alternative response for a more obvious reaction (naming the ink color of a word denoting a different color). Consists of 3 stimulus cards containing 100 words, 100 colored rectangles and 100 color-words, respectively.	Executive function
	D2 Test	30,31	Test consists of rows of letters randomly interspersed with a designated target letter. Subject must cross out all target letters.	
	WAIS Digit Symbol	30,31	Involves a symbol substitution task. Consists of pairing numbers to nonsense symbols as quickly as possible.	Visual-motor coordination, psychomotor performance
	WAIS Digit Span	8,29-31	Involves forward and backward repetitions of series of digits (4-8 digits in length read aloud by examiner). Scores are number of digits repeated correctly before 2 failed attempts.	Memory
	Lafayette Clinical Repeatable Neuropsych Test for Digit Vigilance	29	Patients are presented with 2 pages of 59 rows and 35 numbers. Must cross out every target number (6 or 9) as quickly and accurately as possible.	
	Symbol Digit Modalities Test	32	Must substitute numbers for geometric symbols according to a key. Score is number of correct responses within 90 seconds.	Processing speed and vigilance
	Necker Cube Pattern Control Test	32	Involves a 3 dimensional wire cube that can be viewed from two different perspectives due to spontaneous perceptual reversals of the foreground and background. Must maintain focus on one of the patterns. Score is percent reduction in pattern reversals from a 30 second baseline to a second 30 second holding condition where patient is instructed to hold one pattern for as long as possible.	

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Table 2. Continued

Type of Test	Test Name	Citations	Description	Domain Overlap
Memory	RBMT	18	11 items involving remembering to carry out some everyday tasks or retaining information required for adequate everyday functioning.	
	RBMT Paragraph Recall Subtest	29	Brief paragraph (5 sentences in length) is presented. Participants must recall as many ideas as they can from the paragraph.	
	WMS Logical Memory	22,33	Tests immediate and delayed recall from a short paragraph.	
	WMS Visual reproduction Subtest	30	Must reproduce 4 geometric designs from memory. Each design is shown for 10 seconds. After a 20 minute delay, must draw the figures from memory again.	
	WMS Letter-number Sequencing	33	Must reorder sequences of letters and numbers first in ascending order and then with the letters in alphabetical order.	
	WMS Digit Span	33	Similar to WAIS Digit Span.	Attention and concentration
	WMS Spatial Span	33	Must reproduce spatial patterns, first in the same and then in the reverse order of presentation.	
	WMS Facial Recognition Subtest	22	Rapid presentation of series of closely cropped faces. Must identify which faces were previously seen immediately after presentation and again after 30 minute delay.	Visuospatial

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Table 2. Continued

Type of Test	Test Name	Citations	Description	Domain Overlap
Memory (continued)	RAVLT	22,29-31,33	List of 15 words is presented 5 times. Must attempt free recall of the list after each presentation. A 15 word interference list is then presented followed by free recall of the interference list and then the original list. A 20 minute delay is followed by free recall of the original list. Scored by total number of words recalled.	
	RCFT	22,29-31,33	Must copy a complex geometric design and then reproduce the design after delays of 3 minutes and 30 minutes.	Visuospatial
	California Verbal Learning Test	22	Must memorize a shopping list and recall the list after a time delay and presentation of an alternate list.	
	Warrington Recognition Memory Test	22	Presentation of single-syllable words as well as a series of male faces. Must indicate whether or not stimulus has been presented previously.	
Executive Function	Stroop test	30,31,33	Patient must substitute alternative response for a more obvious reaction (naming the ink color of a word denoting a different color). Consists of 3 stimulus cards containing 100 words, 100 colored rectangles and 100 color-words, respectively.	Attention and concentration
Processing Speed and Vigilance	Fepsy visual reaction test	30	Computerized test. Stimuli (such as the white square) are presented at random intervals.	Motor function
	Fepsy binary choice test	30	Computerized test. Must react differently to a red square presented on the left side of the screen than to a green square presented on the right.	Motor function

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Table 2. Continued

Type of Test	Test Name	Citations	Description	Domain Overlap
Processing Speed and Vigilance (continued)	Fepsy visual searching test	30	Computerized test. Consists of finding 1 grid pattern out of 24 that matches the one in the center of the screen. Must find 24 different grid patterns.	
	PASAT	22	Increasingly rapid series of numbers are presented. Requires manipulation of pairs of numbers.	Attention and concentration
	Trail-making test B	22	Must consecutively connect alternating series of numbered and lettered circles.	Attention and concentration
	Symbol Digit Modalities Test	22	Must substitute numbers for geometric symbols according to a key. Score is number of correct responses within 90 seconds.	Attention and concentration
Motor Function	Fepsy finger tapping test	30,31	Speed of finger tapping is measured for index fingers of right and left hand separately. Test is repeated 5 tines for periods of 10 seconds each.	
	Fepsy visual reaction test	31	Computerized test. Stimuli (such as a white square) are presented at random intervals.	Processing speed and vigilance
	Fepsy binary choice test	31	Computerized test. Must react differently to a red square presented on the left side of the screen than to a green square presented on the right.	Processing speed and vigilance
	Grooved peg board	29	Utilizes board with 25 randomly positioned slots. A set of pegs must be rotated to be inserted correctly into matching slots, one at a time and as quickly and accurately as possible. Dominant and nondominant hands are tested.	
	Trail-making test A	29	Must draw lines to connect consecutively numbered circles.	Attention and concentration

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Table 2. Continued

Type of Test	Test Name	Citations	Description	Domain Overlap
Language	Dutch Aphasia Society Word Fluency subtest	31	Must generate as many words as possible from a specific semantic category within a limited amount of time.	
	Boston Naming Test	22	Presentation of items depicted figurally. Must name the items.	
	Controlled Oral Word Association	22	Must generate as many words as possible beginning with a specific letter within a time limit.	
	Token Test	22	Must comprehend simple and increasingly complex verbal commands using tokens that vary by shape and color.	
Visuospatial Ability	RCFT	22,29	Must copy a complex geometric design and then reproduce the design after delays of 3 minutes and 30 minutes.	Memory
	Facial Recognition Test	22	Rapid presentation of series of close cropped faces. Must identify which faces were previously seen Immediately after presentation and again after 30 minute delay.	Memory
	Hooper Visual Organization	22	Easily recognizable items are separated into pieces and rearranged. Must reintegrate the pieces into recognizable item.	
Abstract Reasoning	Category Test	22	Must generate hypotheses to discern concepts for 7 subtests. Examiner provides corrective feedback if needed for appropriate modification of the next response.	

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Table 2. Continued

Type of Test	Test Name	Citations	Description	Domain Overlap
Abstract Reasoning (continued)	Raven's Standard Progressive Matrices	22	Presentation of incomplete visual patterns. Must choose the design that completes the pattern from 6-8 choices.	
	WAIS Similarities Subtest	22	Presentation of pairs of verbal stimuli varying from concrete to abstract. Must identify common theme that unites what appears to be disparate items of concepts.	
	Wisconsin Card Sorting Test	22	Must sort decks of cards into piles. Must discern appropriate sorting strategy based on corrective feedback from examiner. At various points the sorting strategy changes and participant must adapt and generate new hypotheses.	
Self-Report of Cognitive Functioning	EORTC QLQ-C30	18,31	Multidimensional QOL instrument. Includes cognitive functioning and global health status scales.	
	Brief Mental Fatigue Questionnaire	18	Rating scale for 9 mental fatigue symptoms on scale of 0-4.	
	FACT-COG	12	Self-report on 36 items for cognitive function and impact on QOL. Includes evaluation of mental acuity, attention and concentration, memory, verbal fluency, functional interference, deficits observed by others, change from previous functioning and impact on QOL.	
	General Health Questionnaire	33	Includes 12 general health items and 25 questions related to lapses in attention in everyday life ranked on 6 point scale (0-5).	

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Table 2. Continued

Type of Test	Test Name	Citations	Description	Domain Overlap
Self-Report of Cognitive Functioning (continued)	Cognitive Problems in Daily Life Checklist	31	Interview regarding memory, attention, thinking and language issues encountered in daily life. Scored on 5 point Likert scale.	
	Patients Assessment of Own Functioning	29	33 item measure rating general memory and orientation, language/communication, memory, cognitive/intellectual and sensory-motor domains on 6 point scale.	
	Attentional Functional Index	8	Uses 16 linear analogue scales to self rate effectiveness in cognitive activities such as planning daily activities, getting started on tasks, making decisions, keeping a train of thought, remembering to do important things and attending to details.	

Abbreviations: WAIS: Wechler Adult Intelligence Scale; PASAT: Paced Auditory Serial Addition Task; HSCS: High Sensitivity Cognitive Screen; RBMT: Rivermead Behavioral Memory Test; WMS: Wechler Memory Scale; RAVLT: Rey Auditory-Verbal Learning Test; RCFT: Rey-Osterrieth Complex Figure Test; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QOL: quality of life.

Table 3. Neurocognitive tests shown to be sensitive to CRCI in patients with breast cancer[9]

Domain	Test	Effect Size
Language	HSCS Language Subtest	Small
Motor Function	Grooved Pegboard	Large
	Fepsy Finger Tapping Test	Moderate
Visuospatial skill	RCFT Copy Test	Moderate
	WAIS Block Design Subtest	Moderate
Verbal Memory	HSCS Memory Subtest	Small

normal range. However participants' acknowledge losses in cognitive ability that have significant impact on quality of life.[20]

Assessment of cognitive function in participants with cancer is further complicated by a number of potentially confounding variables such as age, education, hormonal status, anemia, fatigue, anxiety and depression.[3] Controlling for these factors still yields the independent presence of cognitive change in patients who have received chemotherapy. However, age and education are significant predictors of cognitive performance and depression is positively correlated with patients' self-report of cognitive changes.[8] Cimprich et al[8] studied pretreatment factors related to cognitive functioning in newly diagnosed women with breast cancer. Cimprich et al[8] noted that younger women may have perceived even small fatigue-related losses in attention that interfered with usual levels of functioning but were not detectable on testing. Older women demonstrated decreased ability to direct attention prior to any treatment and thus may be at higher risk for treatment-related changes in cognitive function. Hypotheses generated about the discrepancy between self-report and objective testing include the rationale that subjective measures reflect perceived changes while objective measures only assess current performance and do not reflect changes over time. Thus subjective measures may be sensitive to smaller effect sizes than those of objective measures available today.[21]

The traditional neusopsychogic battery may take anywhere from 4-7 hours to administer and requires extensive training in administration and scoring.[22] The length of time needed raises additional challenges.[3] Patients receiving treatment or recovering from treatment for cancer commonly experience significant fatigue. Finding a balance between tests that yield clinically significant results with those that are not unduly burdensome for patients and investigators is also a barrier to prospective research.[23] Lengthy testing also adds cost in time and personnel to clinical trials.

Conclusion

Substantive work remains to be done to identify the neuropsychological tests most sensitive to CRCI and to develop new tests more closely related to real-life situations where cognitive changes are noted.[24] Accurate quantification of the incidence and duration of CRCI across cancer diagnoses would yield valuable information related to the associated risk factors. Ultimately, identification of the populations at risk may lead to the development of appropriate interventions and/or preventative strategies. Additionally, the ability to provide realistic expectations of chemotherapy-associated sequelae would enhance the process of informed consent.

The importance of assessing patients' perceptions of cognitive change cannot be ignored.[4] Self-report of patients' perceptions may be more sensitive to subtle deficits than standard neuropsychologic tests.[19] Patients' description of the lived experience of CRCI may provide rich data that is useful in more accurately defining the types of cognitive changes that result from chemotherapy. Ahles and Saykin[1] noted that quantitative instruments may glean less rich data about the cancer experience. They offered the example of comparing a quantitative survey yielding information that

a patient was able to work in the same profession following chemotherapy to the information that could be gleaned from a qualitative assessment whereby one may learn that the decision was made to move to a less demanding position or not to compete for a promotion due to impairment of cognitive function.[1]

Patients' descriptions of their perceptions of the phenomenon could prove to be useful for the revision of current neuropsychologic tests to achieve more ecologic validity or to develop new tests that are more sensitive to the subtleties of CRCI. A deeper understanding of the patients' experience may also provide insight into the development of appropriate interventions for preventing or minimizing these affects as well as the identification of effective coping strategies. A gap in the literature exists re: the patients' lived experience of the CRCI phenomenon. Thus, there is need for qualitative research to more thoroughly describe the phenomenon.

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Chapter 10

Imaging as a Means of Studying Chemotherapy-Related Cognitive Impairment

Robert B. Raffa*

Abstract

The chemotherapy-related cognitive impairment (chemo fog/chemo brain) that is reported by many cancer patients is supported to varying degrees primarily by evidence from prospective and retrospective clinical studies. However, the inherent difficulty in conducting such trials (including ethical issues of placebo-controlled designs), the fact that the cognitive impairment is characteristically subtle and that the patients might be able to compensate for their deficits during testing, gives rise to questions about the degree and the extent of the problem—and indeed even if there is a problem. Neuroimaging techniques might offer additional insight. This chapter is a succinct summary of a more expanded review of the relatively few such studies.[1]

Introduction

According to individual cancer survivors (see Chapter 2) and a variety of studies using different designs,[2-8] a significant, but unknown percentage, of cancer survivors who have undergone treatment with chemotherapeutic agents have subtle, but noticeable, deficits in cognitive performance.[9-16] The particular domains of cognitive deficits have been described,[9-13] as have the negative impact on the quality of life of the increasing number of breast-cancer survivors.[17-18] Unfortunately, the inherent or methodological difficulties in the clinical studies leave a number of uncertainties about the problem.[19-21]

An alternative to such studies are electrophysiological or imaging studies. They might offer a more objective approach, in the sense that they might be less susceptible to extraneous factors. They might also be free of the compensation that patients might use in other test settings. There are only a few such studies to date.

Electrophysiological Studies

There are two reports of electrophysiological changes in breast-cancer survivors who had undergone treatment with adjuvant chemotherapy.[22,23] In one of these studies, 26 patients had received a regimen of cyclophosphamide, 5-FU and methotrexate about four to six years prior to the study. Half of the group had also received tamoxifen. The chemotherapy-treated group displayed differences from the control group (breast-cancer survivors not treated with chemotherapy, instead treated with surgery and radiotherapy) on a visual information-processing task.[24-26] The difference was interpreted as reflective of a shorter duration of stimulus evaluation processes and more

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problems with energetic aspects of information processing in the patient group. Similar differences were noted in the other study of breast-cancer survivors (about 4 years) who had been treated with an adjuvant chemotherapy regimen (conventional-dose cyclophosphamide/epirubicin/5-FU or high-dose cyclophosphamide/thiotepa/carboplatin) compared to controls (breast cancer patients not treated with chemotherapy). The authors concluded that the difference was due to "suboptimal phasic cortical arousal and problems with the allocation of processing resources".

A small set of studies have added a new way of addressing this issue by utilizing neuroimaging techniques—such as PET (positron emission tomography), MRI (magnetic resonance imaging) and others—to examine brain structure/function of breast-cancer survivors. The results of this approach from representative studies are summarized briefly below.

Neuroimaging Studies

A series of studies compared MR (magnetic resonance) and proton spectroscopy imaging of the brains of women (mean age 47.3 years) with Stage II to IV breast-cancer who had received high-dose adjuvant chemotherapy with cyclophosphamide, cisplatin and carmustine preceded by induction chemotherapy (doxorubicin, fluorouracil and methotrexate) and followed by autologous hematopoietic progenitor stem cell transplant (none had cranial X-radiation) to normal controls.[27-29] The observed differences, which was attributed to the chemotherapy, consisted primarily of white matter abnormality (Figs. 1, 2). The time course of the changes was interesting. They were evident at about 2 months, reached a plateau at about 6 months and persisted for the duration of the period of observation (about 1 year). The authors concluded that the observed imaging differences suggested that the effect of high-dose chemotherapy is predominantly on the water spaces of the white matter of the brain and that the underlying neuronal damage or dysfunction is most likely minor (this being consistent with the good global cognitive ability of these patients).

Two studies used MRI to examine the brains of breast-cancer survivors who had been treated with various regimens and combinations of carmofur, cyclophosphamide, doxifluridine, doxorubicin, epirubicin, 5-FU, methotrexate, paclitaxel, or tegafur uracil.[30,31] Although the first study did not find any significant chemotherapy-related difference in hippocampal volume,[30] volume differences in the cingulate gyrus, superior and middle frontal gyri, parahippocampal gyrus and precuneus were observed at one (but not three) years.[31]

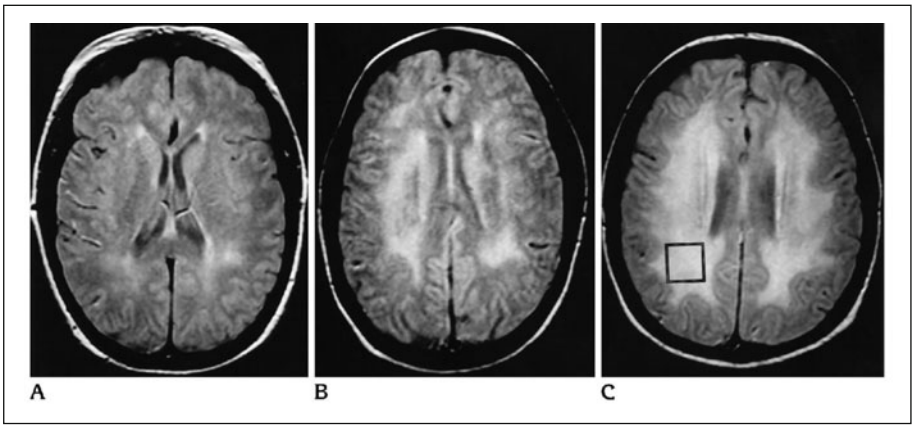

Figure 1. Mild (A), moderate (B) and severe (C) T2 hyperintense white matter change at the level of the lateral ventricle in high-dose chemotherapy—treated patients, corresponding to white matter change per brain of 12, 62 and 153 cm^3, respectively. (The *box* in C indicates the location of the spectroscopy voxel). Figure reprinted from: Brown MS et al. Amer J Neuroradiol 1995; 16:2013-2020,[28] with permission from the American Society of Neuroradiology.

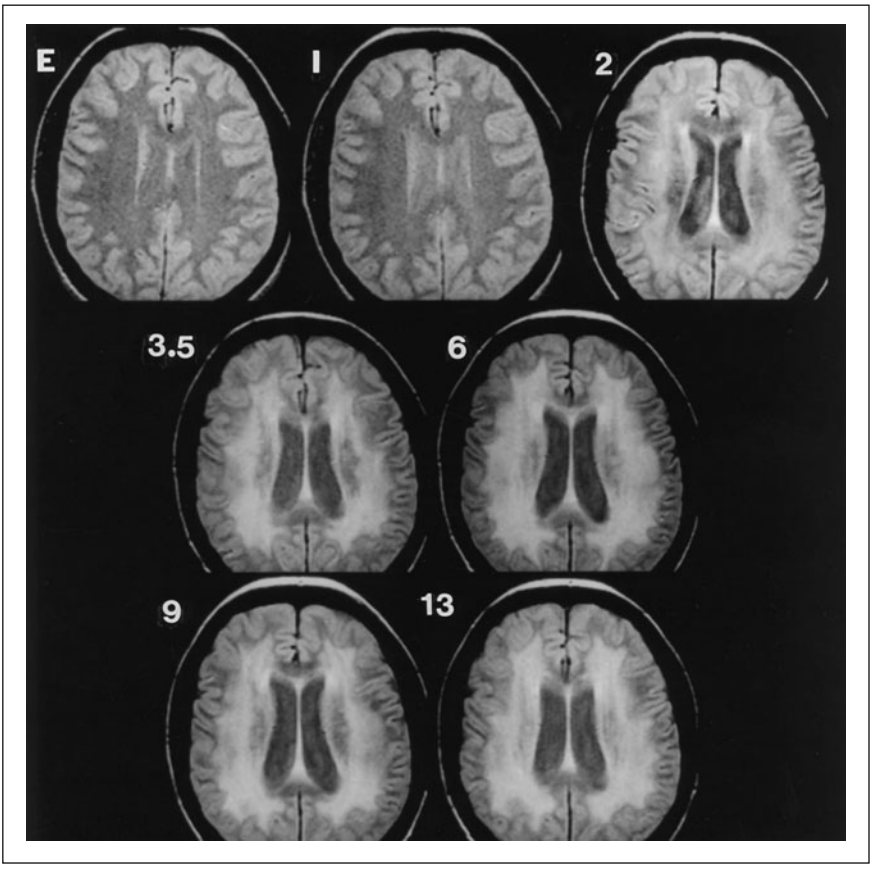

Figure 2. Abnormal progressive increase in white matter after induction of chemotherapy (I) and at 2, 3.5, 6, 9 and 13 months after treatment compared to entry (E). Figure reprinted from: Brown MS et al. Amer J Neuroradiol 1998; 19:217-221,[29] with permission from the American Society of Neuroradiology.

There is also a fascinating and rare, study of twins.[32] The subjects of the study were 60 year-old monozygotic twin sisters who had been reared together. One of the twins had received chemotherapy as part of her treatment for breast-cancer, whereas the other twin had no history of cancer. The chemotherapy-treated twin had substantially more cognitive complaints, yet there were only minimal differences between them on standardized neuropsychological tests. Functional MRI (Fig. 4) revealed that the more affected twin "... demonstrated a much broader spatial extent of activation in typical working memory circuitry (bifrontal and biparietal regions)" than did the untreated twin. This is strong evidence in favor of the idea that patients are capable of compensating on standardized neuropsychological tests and do so. It also suggests that imaging is a more discriminating tool to evaluate chemotherapy-induced damage.

In the first PET (positron emission tomography) (^{15}O) study of regional brain activity of breast-cancer survivors who had received chemotherapy 5-10 years prior,[33] significant differences between the chemotherapy-treated group and controls that did not receive chemotherapy were in the inferior frontal gyrus and the contralateral posterior cerebellum near midline (Fig. 4A). The region that correlated most significantly with impaired cognitive performance (in a short-term memory recall task) was in the left inferior frontal cortex (Fig. 4B).

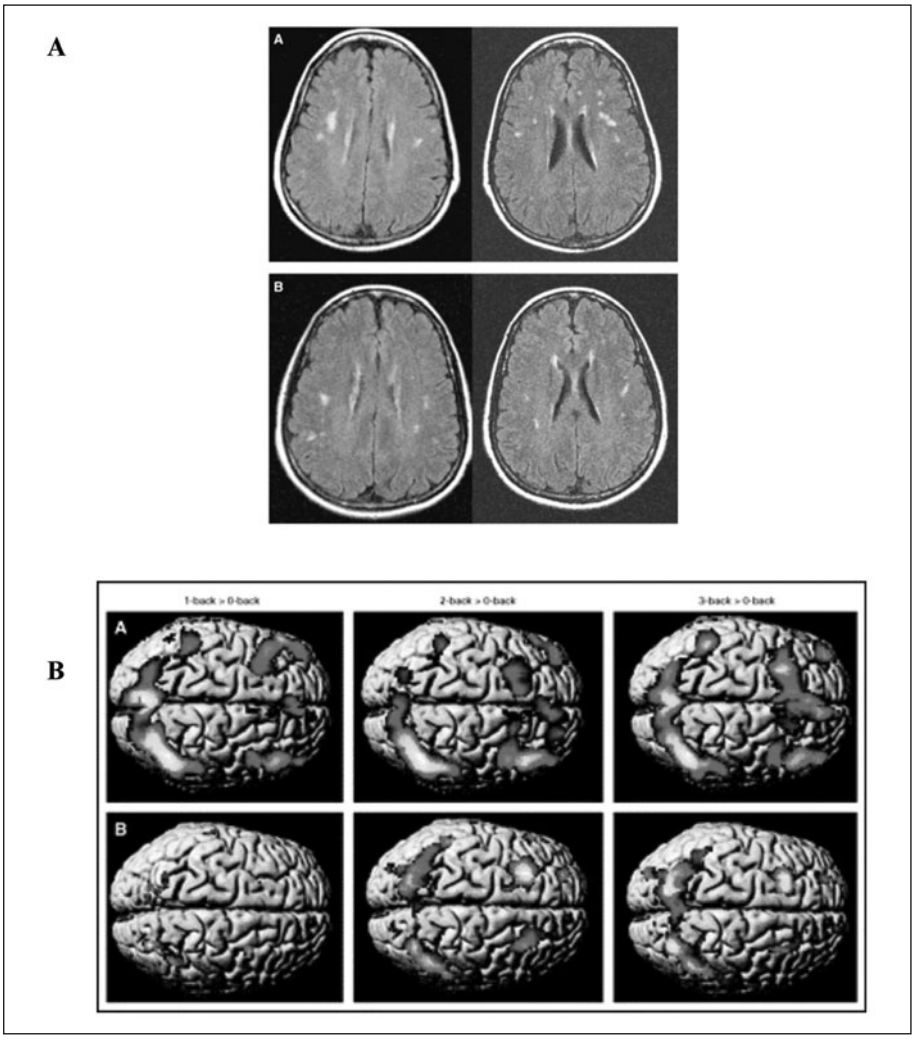

Figure 3. A) MRI of white matter hyperintensities in chemotherapy-treated 60-year-old identical twin (scans labeled A) compared to the twin who did not receive chemotherapy (scans labeled B). B) fMRI of the twins solving an incrementally increasing level of difficulty (left to right) working-memory task (colored regions denote increased brain activation). Figure reprinted with permission: ©2007 American Society of Clinical Oncology. All rights reserved. Ferguson RJ et al. J Clin Oncol 2007; 25:3866-3870.[32] A color version of this image is available at www.landesbioscience.com/curie

Conclusion

Clinical studies provide seemingly consistent evidence of cognitive dysfunction in patients treated with chemotherapeutic agents. But two recent reports either "... failed to confirm previous reports suggesting adjuvant chemotherapy is associated with problems in cognitive functioning among women who receive treatment for Stage 0 to II breast carcinoma" or that only "... a few women experience objective measurable change in their concentration and

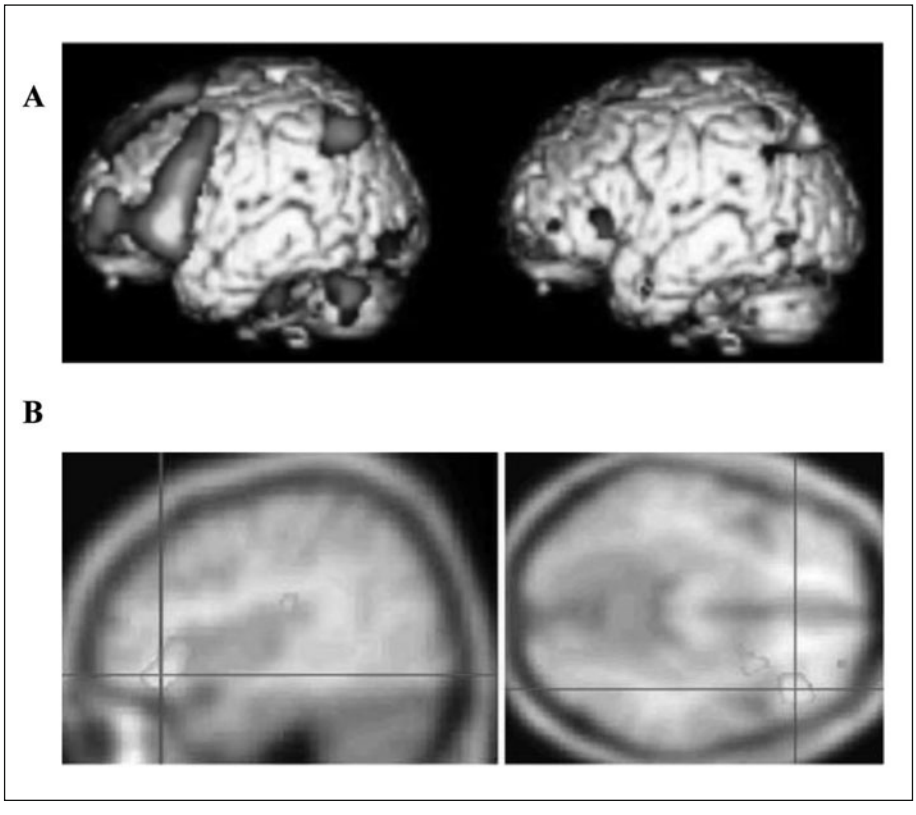

Figure 4. A) Significant activation associated with short-term recall occurred in the inferior frontal gyrus (bright yellow area in left image) in chemotherapy-treated patients (left), but not untreated patients (right), who showed more significant activation in the parietal cortex (bright yellow area in right image). B) Statistical parametric maps (sagittal, left; transaxial, right) identifying areas where brain metabolism correlates (yellow voxels superimposed on an average MR T1-weighted image for anatomical reference) with cognitive performance in chemotherapy-treated subjects. The cursor lines intersect at the voxel of peak significance, located in the left inferior frontal cortex. Figure reprinted with permission from: Silverman DHS et al. Breast Cancer Res Treat 2007; 103:303-311.[33] A color version of this image is available at www.landesbioscience.com/curie

memory following standard adjuvant therapy ... the majority [are] either unaffected or even improve over time".[19,21]

Electrophysiological and imaging studies might provide a more objective way of assessing potential deficits induced by adjuvant chemotherapy agents and provide a more definitive answer. There are only a small number of such studies to date, but they are relatively consistent in showing specific structural or functional changes, albeit minor, that provide plausible explanation for, or correlation with, the reported minor and specific cognitive impairments. Although electrophysiological and imaging studies have their own limitations, they add new tools to the investigation of chemo fog/chemo brain. In conjunction with the information obtained using other techniques, the information obtained from these studies will hopefully provide objective data and help resolve some unanswered questions.

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Chapter 11

Chemotherapy Associated Central Nervous System Damage

Jörg Dietrich*

Abstract

Chemotherapy is commonly associated with harmful effects to multiple organ systems, including the central nervous system (CNS). Neurotoxicity may manifest as both acute and delayed complications, which is particularly a concern for long-term survivors. Patients may experience a wide range of neurotoxic syndromes, ranging from neuro-vascular complications and focal neurological deficits to generalized neurological decline with cognitive impairment, cortical atrophy and white matter abnormalities.

Along with the use of more aggressive and combined treatment modalities and prolonged survival of cancer patients, neurological complications have been observed with increasing frequency. The mechanisms by which cancer therapy, including chemotherapy and radiation, result in neurological complications, have been poorly understood. Recent studies have now started to unravel the cell-biological basis for commonly seen neurotoxic syndromes and have provided compelling explanations for delayed neurological complications, such as cognitive decline, progressive myelin disruption and brain atrophy.

Introduction

Many cancer patients receive a combination of multiple treatment modalities, including radiation and chemotherapy. In contrast to the well-documented toxic effects of brain radiation that have been recognized for a long time,[1-5] the mechanisms underlying toxic adverse effects of systemic chemotherapy on the central nervous system (CNS) have not been well characterized.

As both systemic chemotherapy and brain radiation can be associated with significant neurotoxicity, patients treated with both modalities are at increased risk to develop neurotoxic adverse effects. For example, cognitive impairment has long been observed in children treated with chemotherapy and radiation for brain tumors[3-5] and other types of cancer.[6,7]

Increasing survival rates of adult cancer patients in recent decades and systematic analysis of cancer survivors in longitudinal studies using neuropsychological testing have revealed compelling evidence that systemic chemotherapy alone can be associated with significant long-term impairment of cognitive function.[8-17] Moreover, systematic imaging studies with computed tomography (CT), magnetic resonance imaging (MRI), functional MRI and positron-emission-tomography (PET) imaging have provided additional evidence that structural and functional CNS changes occur in a significant number of patients treated with chemotherapy alone.[18,19]

Neurotoxic side effects have been observed with nearly all categories of chemotherapeutic agents.[13,20,21] Despite the large number of clinical studies and case reports documenting both acute

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and prolonged neurotoxicity following anticancer treatment, surprisingly little has been known about the cellular mechanisms underlying such damage to the nervous system.

CNS complications of chemotherapy may be the result of direct toxic effects of the drug on the cells of the nervous system, or caused indirectly through metabolic abnormalities, inflammatory processes, or vascular adverse effects.

The identification and detailed characterization of neural stem cells and diverse progenitor cell populations in the mammalian brain over the past decade have allowed to study the effects of systemic chemotherapy on specific cellular populations and lineage systems. These studies have demonstrated that conventional chemotherapeutic agents, such as cisplatin, cytosine arabinoside, carmustine and 5-fluorouracil, are toxic to dynamic neural progenitor cell populations critically important for the maintenance of normal brain function, white matter integrity and neurogenesis.

Moreover, neural progenitor cells frequently appear to be even more sensitive than cancer cells to diverse chemotherapeutic agents at concentrations used in clinical practice. These cell-biological studies have provided a scientific foundation for frequently observed neurotoxic adverse effects following cancer therapy. In addition, these studies have offered a compelling explanation for progressive and delayed neurotoxicity in cancer patients, such as cognitive impairment and white matter disease.

Stem Cells, Progenitor Cells and Lineage Systems within the Central Nervous System

Cancer therapy can be harmful to a wide range of normal cell types. Importantly, damage to immature cell types, such as to stem cells and progenitor cells, is likely to have a more profound impact on cellular plasticity and on the long-term outcome than isolated damage to more mature and differentiated cell types, which may be replenished from immature progenitor cells.

In order to understand cancer treatment related nervous system toxicity on a cellular level, it is important to be familiar with the current concept of the various cell types and their lineage relationships within the CNS, including neural stem and progenitor cells, mature glia cells and neurons.

Stem cells and their progeny orchestrate the development and regeneration of mammalian tissues. They are found in most organ systems, including the brain. Neural stem cells (NSCs) have the ability for self-renewal, to proliferate extensively and to differentiate into multiple neuroectodermal lineages.[22-24] Through the hierarchical generation of committed progenitor cells,[25,26] NSCs are able to generate all major cell types of the CNS—neurons, astrocytes and oligodendrocytes (Fig. 1). Progenitor cells are restricted in their differentiation potential, although they still may be able to give rise to more than one cellular lineage. For example, glial-restricted progenitor (GRP) cells are able to give rise to both oligodendrocytes—the myelin forming cells of the central nervous system—and astrocytes.[26,27] Neuron-restricted precursor (NRP) cells are able to generate a variety of different kinds of neurons, but not glia. Progenitor cells also have the ability for self-renewal, but this capacity is limited when compared with NSCs. The adult nervous system harbors abundant progenitor cell populations representing a large pool of dividing cells.[28,29] NSCs and neural progenitor cells are critically important during development, but also appear to be vital in the physiology and integrity of the adult brain. Strikingly, NSCs persist throughout lifetime within specifically organized neurovascular niches,[30-34] supporting ongoing neurogenesis and gliogenesis. During development, stem cells are found in the ventricular zone of the CNS. In the adult brain, NSCs are primarily restricted to two major germinal zones, the subependymal zone of the lateral ventricles and the subgranular zone of the dentate gyrus within the hippocampus.[24,33,35] Under physiological circumstances, NSCs comprise a relatively quiescent cell population, however, these cells have the potential to proliferate and migrate extensively, characterizing the adult brain as a surprisingly dynamic organ system.

The persistence of NSCs in the adult brain reflects their role in endogenous repair mechanisms and maintenance of normal brain functions.[36-39] Consequently, the disruption of neural stem and progenitor cells, e.g., through cytotoxic therapy, might result in critical impairment of neurological function. Importantly, toxicity on the level of progenitor cells offers an explanation for long-term

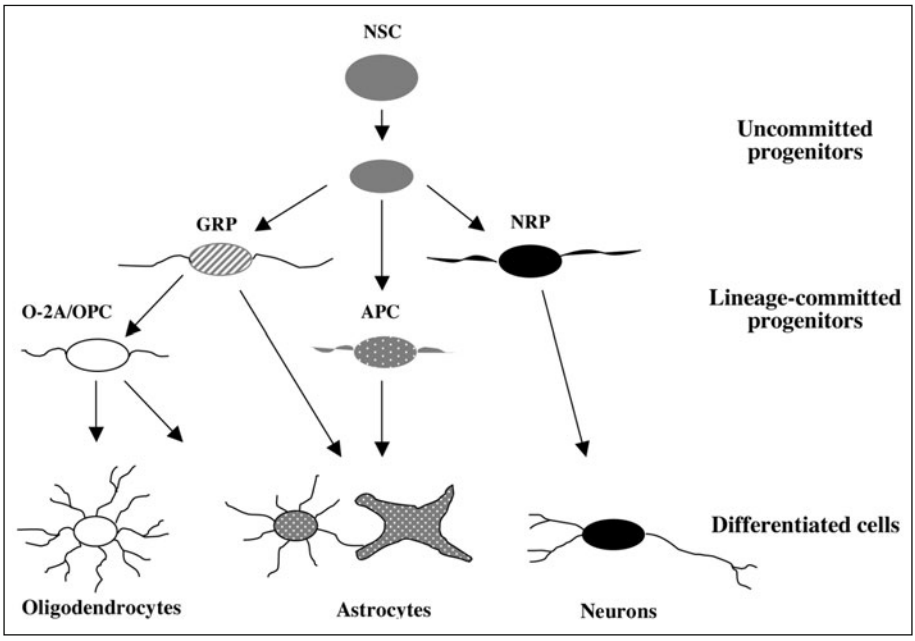

Figure 1. Stem cells, progenitor cells and lineage relationships in the mammalian central nervous system. The diagram gives an overview of the complex lineage relationships between both immature and mature cell types in the central nervous system. Multipotent neural stem cells (NSCs) give rise to neurons, astrocytes and oligodendrocytes through hierarchical generation of intermediate or lineage-committed progenitor cell populations. Tripotential glial-restricted precursor cells (GRP) have the potential to differentiate both into astrocytes and oligodendrocytes through the generation of bipotential oligodendrocyte Type 2 astrocyte (O-2A) cells (also known as oligodendrocyte precursor cells (OPC)). Mature astrocytes may be generated from astrocyte precursor cells (APC) and mature neurons may be generated via neuron-restricted precursor cells (NRP).

neurological adverse effects, such as cognitive impairment, white matter degeneration and cerebral atrophy.[39-43] The following sections will summarize the current understanding of cellular toxicity as the consequence of cancer therapy and will discuss how specific cellular toxicities might be linked to commonly seen neurologic complications.

Cell-Biological Analysis of Chemotherapy Associated Brain Damage

Patients treated with localized or systemic chemotherapy are at risk of developing a wide spectrum of possible neurotoxic adverse effects and survival is commonly associated with the price of long-term neurological complications.[21,44,45] Neurotoxic syndromes can present as acute, subacute, or delayed effects—even years after cessation of treatment. Such delayed neurologic complications may include varying degrees of cognitive impairment, white matter disease, cerebral atrophy and dementia.[9,10,17,21,46,47]

Neurotoxic side effects have been observed with a wide range of chemotherapeutic agents, including alkylating agents (e.g., carmustine and cisplatin), antimetabolites (e.g., cytosine arabinoside, 5-fluorouracil and methotrexate), mitotic inhibitors (e.g., vincristine) and antihormonal agents (e.g., tamoxifen),[13,20,21,45,48] although some compounds appear to have a higher neurotoxic potential than others. Methotrexate and carmustine (BCNU), for instance, are associated with a relatively high frequency of neurotoxicity, which may be severe and progressive, especially if the

Table 1 Chemotherapeutic agents shown to target neural progenitor cells and oligodendrocytes in experimental studies

- Carmustine (BCNU)
- Cisplatin
- Cyclophosphamide
- Cytosine arabinoside (Ara-C)
- 5-Fluorouracil (5-FU)
- Ifosfamide
- Methotrexate
- Misonidazole
- Thiotepa

drug is administered after radiation therapy. Both agents may cause a well-described leukoencephalopathy syndrome, particularly when administered at high dose, intrathecally, or in combination with cranial radiotherapy.[49-52]

Until recently, the detailed cellular mechanisms for the wide spectrum of long-term neurological adverse effects following chemotherapy have been largely unknown. There is now compelling evidence that many chemotherapeutic agents directly target the normal cells of the nervous system (Table 1). Despite a large number of patients receiving chemotherapy, some patients are clearly more affected by CNS toxicity than others, suggesting that beside direct drug effects on cellular viability, other mechanisms are likely to play important roles in modulating the potential risk to develop CNS toxicity.

The majority of conventional anticancer agents exert nonspecific toxic effects on a diverse range of normal cell types affecting multiple organ systems. While treatment related toxicities have probably been most extensively studied in the hematopoietic system, there is no comparable level of analysis for most other organ systems, including the brain. The conventional view has been that cytotoxic drugs preferentially target rapidly dividing cells. More recent studies on the effects of chemotherapy on the brain indicate, however, that the mechanisms of neurotoxicity are far more complex than simply toxic effects on proliferating cells.

Early morphological studies on rats exposed to methotrexate and misonidazole suggested that glial progenitor cells might be particularly vulnerable to cytotoxic agents.[53] Local application of methotrexate into the ventricular system resulted in destruction of the ependymal cell layer and ventricular dilatation. In addition, dying glial cells were observed in the gray and white matter along with microglial activation. A significant reduction in cell density and number of mitotic cells was demonstrated in the anterior subependymal plate just 1-2 days after methotrexate administration.

Other studies provided additional experimental evidence that numerous cytotoxic agents, including cyclophosphamide, cisplatin, ifosfamide and thiotepa were associated with significant and dose-dependent neurotoxicity, visible in multiple brain regions, including cortex, basal ganglia and hippocampus.[54] These studies, however, did not provide information on the lineage-specific effects of chemotherapy on the brain.

It had been suggested that the oligodendroglial lineage might be in particular vulnerable to alkylating agents,[55] consistent with the clinical observation that oligodendrogliomas and astrocytomas typically show a differential response to chemotherapy.[56]

Using a detailed lineage-based approach to test the effects of commonly applied chemotherapeutic agents on mature and immature cell types of the nervous system, it has been shown that dividing neural progenitor cells, which are the direct ancestors of all differentiated cell types of the CNS and oligodendrocytes are the most vulnerable cell populations to the effects of multiple chemotherapeutic agents.[42] Vulnerability was not restricted to dividing cells, as nondividing oligodendrocytes were as sensitive than oligodendrocyte precursor cells.

Alarmingly, the degree of sensitivity of normal progenitor cells and oligodendrocytes to carmustine, cisplatin and cytosine arabinoside surpassed the sensitivity of cancer cells from different tissues when applied at drug concentrations detectable in the cerebrospinal fluid in patients. In contrast, dividing astrocytes and mature neurons were less vulnerable when compared with the degree of sensitivity of oligodendrocytes and neural progenitor cells.

Even transient exposure to minimal doses of BCNU and cisplatin that were not associated with cell death in cell culture resulted in suppression of cell division and increased differentiation of progenitor cells. Such a loss of dividing cells and reduction of the overall progenitor cell pool would compromise the ability of dividing progenitor cells to contribute to repair processes and could also contribute to long-term or delayed toxicity.

In vitro results were predictive of in vivo effects. Single systemic exposure to chemotherapy resulted in significant posttreatment impairment of cell proliferation and increased apoptosis of oligodendrocytes and neural progenitor cells; however, this initial response was followed by a marked rebound in cell proliferation in the subventricular zone, the dentate gyrus and corpus callosum. This rebound in cell division of progenitor cells was significantly diminished following repetitive drug exposure, which resulted in long-term suppression of cell division in the germinal zones and large white matter tracts of the CNS.[42]

Subsequent studies provided further cell-biological insights into the perplexing phenomenon of delayed toxicities, as it can be seen with progressive white matter damage following chemotherapy, even years after drug exposure. For example, white matter changes induced by high-dose chemotherapy for breast cancer may have a delayed onset of several months.[19,57] A delayed demyelinating syndrome may be seen in patients treated with chemotherapy regimen containing the antimetabolite 5-fluorouracil.[58-63] Consistent with initial studies on the cellular toxicity of carmustine, cisplatin and cytosine arabinoside,[42] 5-fluorouracil was exceptionally toxic to lineage-committed progenitor cells and oligodendrocytes.[43] Transient exposure to sub-lethal drug concentration was associated with suppression of progenitor cell division. As predicted by cell culture assays, systemic exposure of mice to 5-fluorouracil resulted in increased apoptosis and decreased progenitor cell proliferation for extended periods of time in the germinal zones of the CNS and the corpus callosum. Strikingly, even transient systemic exposure to 5-fluorouracil was associated with a syndrome of delayed and progressive white matter damage six months after initial treatment.[43] Moreover, functional studies using brainstem-evoked potentials confirmed disintegration of myelin fibers as a delayed consequence of 5-fluorouracil treatment.[43]

Neurotoxicity has also been shown in experimental studies to occur after systemic application of thiotepa[64] and methotrexate.[65] Both drugs were associated with a dose-dependent inhibition of hippocampal cell proliferation. In addition, methotrexate has been shown to result in impaired cognitive performance as a functional consequence of chemotherapy associated toxicity.[65,66]

Taken together, damage on the level of neural progenitor cells has offered a compelling explanation for the frequently seen delayed toxicities in patients, such as progressive dementias and leukoencephalopathies. It is conceivable that long-term and progressive cognitive decline in cancer survivors are the result of a combination of decreased proliferation of neural progenitor cells, impaired hippocampal neurogenesis and damage to oligodendroglial cells and white matter tracts.

Many open questions remain regarding the effects of chemotherapy on the brain. Most patients are repetitively exposed to a number of different agents and it is not known whether multiple drugs given concomitantly act synergistically on the brain and influence the integrity of the blood-brain-barrier, possibly allowing less lipophilic drugs to penetrate the CNS.

It is also not known, why certain individuals are much more affected than others by the disturbing adverse effects of cancer treatment, suggesting additional factors to play important roles in the manifestation of neurotoxic syndromes. Candidate mechanisms identified to modulate neurotoxicity include genetic polymorphisms that influence the efficiency of DNA-repair mechanisms and drug efflux pump systems.[67-71] Therapy-related changes in cellular redox dynamics and production of reactive oxygen species are also likely to influence the degree of toxic side effects.[72-74] Notably, many chemotherapeutic agents have oxidizing character and are associated with profound changes

in anti-oxidant levels,[75,76] which may persist even years after cessation of treatment.[77] As oxidative balance has been shown to be one of the most critical factors to modulate key cellular functions in stem and progenitor cells,[78] pro-oxidative effects of cancer treatment are likely to influence normal cellular functions in progenitor cells and postmitotic cells. Another factor that may be relevant for progenitor cell function in the CNS is the possible effect of chemotherapy to shorten telomere length and to decrease the lifespan of a dividing cell by senescence and apoptosis.[79-81]

Conclusion

There has been increasing evidence that cancer treatment, including chemotherapy and radiation, may exert direct toxic effects on progenitor cells, oligodencrocytes, white matter tracts, gliogenesis and neurogenesis. Damage to neural progenitor cells has offered a compelling explanation for delayed toxicities, such as cognitive decline, cerebral atrophies and prolonged white matter damage. Clinical and experimental data suggests, however, that additional factors are likely to play a role in modulating the risk and degree of developing neurotoxicity.

Several novel agents, such as angiogenesis inhibitors and molecular targeted therapies have complemented the armament of cancer therapy in recent years.[82] Targeting specific signaling pathways in cancer cells (e.g., EGF, FGF, PDGF and VEGF) may come with the price of undesirable neurological complications in long-term survivors, as the same pathways are critically important in normal stem and progenitor cell physiology.[82]

Future studies will need to identify factors and mechanisms that influence CNS toxicity and will have to design and optimize individual therapies in order to avoid unnecessary toxicities. When compared with the hematopoietic system, where the use of certain growth factors (e.g., GM-CSF, G-CSF, Erythropoietin, etc.) has enabled patients to rapidly recover from treatment related myelosuppression, there are currently no neuroprotective strategies available to enhance endogenous CNS repair. Thus, one of the most important goals of future cancer therapies will be the identification of neuroprotective strategies along with the development of tumor-specific therapies to avoid unnecessary toxicities and to promote endogenous nervous system repair after chemotherapy.

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Chapter 12

Is Systemic Anti-Cancer Therapy Neurotoxic? Does Chemo Brain Exist? And Should We Rename It?

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Abstract

The existence of chemo brain has become almost universally accepted, although many details of the concept are controversial. Data about the different types of cognitive impairment and their duration are not always consistent in the literature. We still do not know which cytotoxic agents are responsible, which characteristics make patients vulnerable and which biologic mechanisms are involved. This chapter reviews the recent literature and provides an actualized definition of chemo brain, including recent functional imaging data and discusses its controversial aspects. Potential underlying mechanisms and their future possible clinical applications in the prevention and treatment of chemo brain are also discussed. These issues are of clinical importance given the prevalence of breast carcinoma, the increased use of chemotherapy as adjuvant therapy, the increasing use of more aggressive dosing schedules and the increasing survival rates. Better-designed future trials should lead to a better definition and understanding of chemo brain and to future therapies.

Introduction

For many years cancer survivors have worried about the 'mental cloudiness' they notice before, during and after chemotherapy. The exact cause of this mental fog or chemo fog noticed for sometime by the patients and commonly called chemo brain is not known, but only recently have studies been done that could start to explain it. Some people report having these symptoms even before they start treatment. Others report it even though they have not had chemotherapy and are getting hormonal treatments. So the term chemo brain may be inaccurate.

There is growing awareness that malignant disease outside the central nervous system (CNS) and the treatment of such malignancies with biologic, immunologic, or hormonal drugs may result in alterations in patients' mental status. Thus, the existence of chemo brain has become almost universally accepted, although many details of the concept are controversial. Mild cognitive impairment (MCI) following adjuvant chemotherapy, however, has been referred to in scientific publications since the late 1980s. The reported rates of chemo brain patients vary widely, reflecting different definitions of this entity. Data about the different types of cognitive impairment and their duration are not always consistent in the literature. We still do not know which cytotoxic agents are responsible, which characteristics make patients vulnerable and which biologic mechanisms are involved.

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This issue is of clinical importance given the prevalence of breast carcinoma, the increased use of adjuvant chemotherapy, the increasing use of more aggressive dosing schedules, the increasing survival rates and patients' natural desire to return to their normal occupational, academic and social pursuits. Most of the time very subtle and durable, this cognitive impairment qualified as 'mild' by physicians, affects daily activities and needs to be researched further. Since chemotherapy-induced MCI is persistent but not fatal, its influence on quality of life (QOL) is important for long-term survivors. Memory loss or attention deficits may drastically affect the ability to fulfill responsibilities, especially for patients who hold professional and social positions. Many chemo brain patients were formerly high functioning individuals who had juggled multiple tasks with ease before chemotherapy. Long-term cognitive impairment is the single biggest complaint related to QOL reported by these patients. In this chapter, an actualized definition of the chemo brain concept is provided, including its controversial aspects. This definition relies on evolving etiological hypotheses, each one representing a potential and emerging therapeutic option.

Towards a Better Definition of Chemo Brain

Self-Reported Cognitive Problems

The manifestations of chemo brain also named chemo fog are often subtle. Cancer survivors may complain of fatigue, lack of focus, mental confusion, inability to concentrate, inability to organize daily activities, loss of memory and memory lapses, decreased mental clarity, trouble concentrating and maintaining attention, trouble remembering details, names and common words, trouble multi-tasking and finishing certain tasks, trouble learning new skills and slower thinking and processing. Self-reported cognitive problems are common among women receiving adjuvant therapy for breast cancer but are most often unrelated to objective cognitive impairment.[1] Shilling et al objectively measured impairment and asked 142 breast cancer patients in the adjuvant setting to speak about the type and extent of problems they encounter in everyday life. They investigated the relationship between self-reported and objective cognitive impairment, QOL and psychological distress. The majority of participants reported problems with their memory (71% overall at 6 months, 60% at 18 months) and concentration (64% and 42%, respectively), e.g., everyday slips and lapses. This was unrelated to objective cognitive performance; rather, it was associated with psychological distress and QOL. An explanation of the discrepancies between self-reported and objective cognitive impairment will be provided below.

Objective Cognitive Impairment and Its Duration

Little is known about chemo brain mechanisms, type, severity and episode length. In most studies, cognitive dysfunction was not rigorously defined. According to recent prospective randomized longitudinal studies, cognitive performance is not related significantly to self-reported cognitive problems, anxiety, depression, chemotherapy induced-menopause, or darbopoetin-administration.[1]

Objective Cognitive Impairment

According to literature data, the most impacted cognitive areas involve subcortical frontal zones with decreased attention and concentration, executive and psychomotor functions. Studies have also reported impairment of verbal learning, psychomotor processing speed, mental flexibility, verbal, nonverbal and visual memory, memory retrieval, confrontational naming, complex visuoconstruction and fine motor dexterity.[2-9]

Duration of Symptoms and Clinical Signs

The greater concern for patients is about the time-duration of these cognitive changes. The data are less clear on this issue, with more recent longitudinal and follow-up studies generally suggesting that the disturbances resolve over time and earlier cross-sectional studies indicating that significant cognitive deficits persist for 1 year or longer in a subgroup of breast cancer patients.[3,4,6,10,11]

For example, while some authors show an improvement of cognitive function as soon as three months or seven months after completion of chemotherapy, MCI is still observed at 2 years after completion by others.[12-14] Some patients recovered at 4 years and it took up to 10 years in others. Using imaging techniques to answer the 'duration' question, we collect again controversial results as illustrated in the section below.[15-17]

It would seem that many of the early, cross-sectional studies tended to over-estimate the risk, severity and duration of cognitive impairment. A recent study is consistent with the few other controlled prospective trials in breast cancer patients in indicating that the cognitive perturbations noted in the short term are no longer evident at 1 year following completion of therapy.[18] Discrepancies among studies with regard to duration of cognitive disturbance probably reflect failure of the cross-sectional studies to account for pretreatment group differences in cognitive function, as well as differences in the choice of control group. These findings underscore the importance of using a controlled prospective design in trying to isolate the cognitive effects of treatments in cancer patients and to assess accurately their duration and extent.

Towards a Better Understanding of Chemo Brain

Can Chemo Brain Occur without Chemotherapy?

Before Chemotherapy

Some skeptics claim that what many patients and doctors consider to be a side effect of chemotherapy may in fact be caused by multiple nonspecific factors. For example mental fogginess could be a result of fatigue secondary to disease, stress, or anesthesia, as well as the combination of non-anticancer drugs.

Impaired cognitive function at baseline in breast cancer patients in the adjuvant setting and spontaneous improvement with time after 'surgery only' are problematic examples.[14] Some prospective studies performed in breast cancer patients in the adjuvant setting and also in Stage III non small cell lung cancer showed a pre-existing statistically significant cognitive impairment at baseline, before starting chemotherapy in 10 to 71% of the studied population.[12-13,19-22] The most significantly affected domains included attention, working memory and verbal learning. Although statistically no significant, nonverbal memory, psychomotor processing speed, confrontational naming, visuoconstruction and upper-extremity fine motor dexterity were impaired more frequently than was expected.

In a prospective study, a cognitive impairment, which was found unrelated to anxiety or depression, was observed before chemotherapy in a subgroup of patients and the rate of decline during chemotherapy (27%) did not exceed the rate of simultaneous improvement (28%).[23] Because the baseline assessment was performed just after surgery and time of diagnosis, which are both very stressful, the authors proposed the hypothesis that the cognitive impairment may be linked to stress-response symptoms. These stress manifestations are different from symptoms and signs of depression and may interfere with performance during cognitive testing. Furthermore, persistent stress-response symptoms and signs also may have caused the cognitive impairment observed during and after chemotherapy in several studies since there is some evidence that posttraumatic stress disorder may be associated with memory and concentration problems. The authors conclude that their results do not corroborate the hypothesis that chemotherapy is the cause of cognitive dysfunction in patients with breast cancer, even if the possibility that chemotherapy participates in this deterioration in a subgroup of patients cannot be ruled out. Hermelink et al[23] propose the alternative explanation that yet unidentified factors affect cognition even before chemotherapy and affect it further during chemotherapy in a subgroup of patients, when another subgroup starts to recover. The authors eventually introduce the renamed concept of 'crisis brain'.

Role of Hormonal Therapy (HT)

It seems essential to determine the exact participation of HT because most of the patients under chemotherapy were also receiving HT in previous studies. There is convincing evidence that estrogen

has a protective role in brain functioning and especially on verbal memory.[24-30] According to Bender et al, the addition of tamoxifen to chemotherapy may lead to more widespread cognitive deficits, with deterioration on measures of visual memory and more memory complaints.[31] The role of HT on cognitive function is also hypothesized or described by others.[12,14,32-34] Recent studies showed that processing speed and verbal memory were also particularly affected by hormonal therapy.[18,32] Functional imaging studies confirmed a significantly decreased metabolism of the basal ganglia in 'tamoxifen plus chemotherapy- treated' patients compared with 'chemotherapy-only' and 'no-chemotherapy' groups.[15] A recent prospective study showed that relative to healthy controls, the anastrozole group showed a nine-fold increase in risk of cognitive decline (as compared to a 5-fold increase in the tamoxifen group).[32] Plasma estrogen levels being significantly lower in women who receive anastrozole compared with those who receive tamoxifen, Bender et al hypothesized, that anastrozole would have a more profound effect on cognitive function than tamoxifen.[31] The results of their cross-sectional study performed in women treated for at least 3 months by HT showed that women who received anastrozole had poorer verbal and visual learning and memory than women who received tamoxifen. The previous findings are consistent with previous reports that estrogen levels and hormone replacement treatment are specifically associated with verbal learning and memory functions in healthy postmenopausal women and with preliminary results from the ATAC trial indicating that adjuvant HT in breast cancer patients primarily affects verbal memory and processing speed.[24-31,35-38]

As highlighted by Collins et al: 'given the fact that the HT can severely deplete estrogen levels, is commonly administered for long periods of time and is being used increasingly in primary preventive settings'. As mentioned by these authors "although subtle", it does not mean "that this effect is clinically nonsignificant. The subtlety of the effects underscores the importance of a controlled prospective design". Authors insist on the critical choice of the control group and on the necessity of a routinely baseline testing prior HT onset in future studies. An alternative approach proposed by these authors is to control "for confounding disease and treatment variables by studying women at high risk for breast cancer who are taking prophylactic hormonal therapy". It will also be of great interest to compare the cognitive effects of Selective Estrogen Receptors Modifiers (SERMs) that may exert an agonist role in the brain and aromatase inhibitors (AI) that block postmenopausal estrogen synthesis resulting in a near total estrogen depletion throughout the body and that may pose a greater cognitive risk than the SERMs.[31]

Understanding Chemo Brain through Its Physiopathology and Preclinical Studies

Studies show a lack of understanding of what causes chemo brain. Many potential etiologic agents may be responsible for this impairment, it is speculated that both host-related factors and disease-related may be involved. Host-related or soil characteristics consist of genetic polymorphisms, immune reactivity, nutritional factors, hormonal histories, or lack of cognitive reserve. Disease-related or seed factors include tumor gene mutations, induction of pro-inflammatory cytokines and paraneoplastic disorders.

Potential underlying mechanisms remain largely unknown and are under investigation in preclinical models. As mentioned by several authors, several mechanisms have been postulated: direct neurotoxic effects (e.g., injury to neurons or surrounding cells, defects in neural repair and altered neurotransmitter levels, blood-brain barrier permeability, efficiency of cellular efflux pumps); oxidative stress and DNA damage; induced hormonal changes; immune dysregulation and/or release of cytokines; vascular injury and blood clotting in small central nervous system (CNS) vessels and genetic predisposition.[39,40]

Genetic polymorphisms that may render individuals more susceptible to these effects have been incriminated. There is preliminary evidence that women with at least one epsilon 4 allele of APOE may be at greater risk for chemotherapy-related cognitive deficits.[41] Same authors also introduced the notion that genetic polymorphisms related to efficiency of the blood-brain barrier (e.g., differential expression of MDR-1) and the functioning of cytokines (e.g., polymorphisms of IL-6), neurotransmitters (e.g., COMT) and DNA repair mechanisms (e.g., XRCC1) might also be important.[39]

Many cytokines are elevated in subjects who have been treated for colorectal or breast cancer, in the absence of recurrence of disease and their levels are not higher in patients who had received chemotherapy.[40] Cytokine levels might relate to deficits in cognitive function. As mentioned by Miller et al, many factors may trigger the activation of inflammatory pathways in cancer patients, "such as surgery, chemotherapy, and radiation that are all associated with significant tissue damage and destruction, which in turn is linked to activation of innate immune response." Miller et al also discussed the direct role played by cytotoxic agents and radiation on the NFκB pathway and they draw the attention on the fact that "receiving a diagnosis of cancer is one of the greatest stressors conceivable." Authors conclude that the above mentioned factors "place the cancer patient at high risk for the development of inflammation-induced cognitive impairment." Although mechanisms of chemo brain clearly involve a complex interplay of genes, hormones and the immune system, findings suggest that inflammatory factors may play an important role.[42] To provide an extensive view of this aspect of "inflammatory neurocognition", authors finally report the significant negative correlation that has been found between plasma IL-6 and executive function in patients with acute myelogenous leukemia or myelodysplastic syndrome and the neuropsychological side-effects of cytokine-based therapies such as IFN-α and IL-2 including frequent loss of concentration, memory disturbances and word-finding problems.[43-44] Reduced psychomotor speed and concentration difficulties were more specifically attributed to IFN-α and working memory or executive dysfunction to IL-2.[45] These cognitive side-effects normally reverse after treatment; however, remaining cognitive impairment may persist in some cases.[46-47]

Preclinical studies were recently performed in animals, using several cytotoxic agents such as methotrexate, 5-FU, cyclophosphamide, adriamycin, carmustin, cisplatin, cytarabine, thiotepa and ifosfamide.[48-51] They have demonstrated that these agents, administered peripherally, can cause disruption of learning and memory across a variety of tasks (Morris Water Maze, avoidance conditioning, cue-specific and contextual fear conditioning tasks) in both mouse and rat models.[52-55] A decline in the spatial working memory and in performance on tasks that are depending on the integrity of the hippocampus and the frontal lobe was shown. Histological analyses of the brain of animals that received chemotherapy have demonstrated cell death and decreased cell division in structures critical for memory and learning, including the subventricular zone, the dentate gyrus of the hippocampus and the corpus callosum.[48,49] Areas involved in neurogenesis, neural progenitor cells and no-dividing oligodendrocytes were particularly exposed, even at doses inferior to the antitumoral ones. Early extensive lesions (within 24 hours) were evidenced in the cortex, thalamus, dentate gyrus and caudate nucleus.

5-FU induced both acute and delayed damage of myelined tracts, without any underlying chronic inflammation or vascular damage. This drug did not affect the total proliferating cell counts or the percentage of vascular-associated and nonvascular proliferating cells in the dentate gyrus. 5-FU also caused deficits in hippocampal memory that are associated with significantly reduced brain-derived neurotrophic factor (BDNF) and double cortin protein levels in the hippocampus, illustrating alterations in neurotrophin levels and neurogenesis.

Anthracyclines can induce a profound oxidative and nitrosative stress in brain tissues, with downstream consequences of super oxide dismutase (SOD) inactivation.[56] Adriamycin (ADR), produces reactive oxygen species (ROS) in cardiac tissue. However, the effect of ADR in the brain is unclear because it does not pass the blood-brain barrier. Nevertheless, it has been demonstrated that agents like ADR can modulate endogenous levels of cytokines, such as tumor necrosis factor alpha (TNF-α).[57,58] Among potential downstream effects of TNF-α is an increase in generation of reactive nitrogen species (RNS).[59] Tangpong et al, showed that the mitochondrion is an important target of ADR-induced NO-mediated CNS injury and that a high level of MnSOD activity is needed for protection of neuronal cells in conditions where overproduction of ROS or RNS is involved. Thus, prevention of MnSOD inactivation by neutralizing elevated systemic TNF-α or removal of NO production could be effective means for the prevention of ADR-induced CNS toxicity, which may underlie chemo brain.

Understanding Chemo Brain through Electrophysiological Techniques and Imaging

Electrophysiological studies assessing the P-300 event-related brain potential showed a decrease in amplitude (intensity of neural activation) and latency (timing and duration of activation) of P-300 associated with chemotherapy, which is consistent with changes in information processing capacity.[60,61]

In favor of the chemo brain hypothesis, MRI studies using voxel-based morphometry and diffusion tensor imaging confirmed the presence of anatomical brain abnormalities in patients treated with chemotherapy:

- MRI scans performed within 1 year after surgery, in breast cancer patients treated with adjuvant chemotherapy, showed when compared to breast cancer patients who never received chemotherapy or healthy controls, significant volume reductions in brain areas correlated with attention and visual memory performances such as the gray matter of right prefrontal and parahippocampal gyrus and the white matter of bilateral middle frontal gyrus, left parahippocampal gyrus, left precuneus and right cingulate gyrus. The 3-year (after initial surgery) assessment did not show anymore any volumes differences.[16] These results are discordant with other series showing a persisting bilateral reduction of gray matter and subcortical white matter in long-term survivors (more than 5 years after diagnosis) of breast cancer and lymphoma.[17]
- Diffusion tensor imaging was used to assess the integrity of white matter tracts in breast cancer patients complaining of cognitive impairment 3 to 34 months after completing their chemotherapy. All were on hormonal therapy at the time of assessment. Age and education matched women served as controls. Significantly decreased white matter integrity (fractional anisotropy) in the genu of the corpus callosum was observed and correlated with reduced grapho-motor speed.[62]

Functional Magnetic Resonance Imaging (fMRI), [O-15] water and [F-18] fluoro-deoxyglucose-positron emission tomography (PET) were used to study brain areas activity while patients were performing specific neuropsychological tasks.[63-65]

Several patterns could be observed in 'chemotherapy groups' if compared to controls:

- Decreased bilateral anterior frontal activation.
- Broader and increased activation in more posterior bi-frontal and bi-parietal areas.
- Altered modulation of cerebral blood flow in the inferior frontal cortex during performance of the memory task suggesting that greater recruitment of frontal cortical regions was necessary to perform the task.
- Decreased resting metabolism of glucose in the left inferior frontal gyrus, in the contralateral cerebellum and in the basal ganglia.

The altered pattern of frontal activation and rest metabolism could be related to impaired working memory and compensatory mechanisms could explain that despite greater cognitive complaints in the chemotherapy treated patients, task performance (memory and executive function) did not differ between groups. The pattern of increased cortical activity and cerebral blood flow in other areas may represent recruitment of a broader neural network needed to accomplish performance comparable to the controls. As matter of fact, cancer survivors treated with chemotherapy frequently self-report higher levels of cognitive problems but perform within normal limits on neuropsychological tests. Indeed, more diffuse brain activation during a working memory task in chemotherapy patients, even when performance was maintained, was shown on fMRI.[63] These changes in activation patterns reflecting a hypothetical compensation for subtle impairment may underlie patients subjective reports of cognitive disturbance and increased mental fatigue. Within the chemotherapy group, the nondecliners actually showed a greater increase in fatigue than the decliners, who showed significantly higher baseline depression scores, suggesting that factors such as poor stress tolerance may be risk factors for chemo brain. 'Decliners' and 'nondecliners' differed on education, such that lower levels of education seemed to be a risk factor for cognitive decline, in accordance to a previously reported concept of 'cognitive reserve'. This last one relying on the

supposition that patients with more education have greater 'cognitive reserve' and can better tolerate brain injury than those with less education.[66]

Does Chemo Brain Exist?

A New Name for a New Concept

From the previously illustrated examples of this chapter, we conclude that so-called chemo brain or chemo fog is a complex concept and factors such as individual vulnerability, surgery and anesthesia, hormonal therapy, treatment-induced menopause, stress, anxiety, depression, fatigue, supportive care medications, genetic predisposition, comorbid medical conditions and paraneoplastic syndroms may be involved.[22] Furthermore, many studies have differed in their neuropsychological assessment and definition of cognitive impairment. It has been proposed to rename this concept 'Cancer- or Cancer-therapy-associated Cognitive Change' or even 'Crisis Brain'.[23]

New Techniques Bringing an Evolving Concept

Recent imaging studies suggest intriguing hypotheses that will guide future research examining the relationships among self-reported measures of cognitive functioning, performance on neuropsychological testing, psychological baseline state and structural and functional changes in patients experiencing cognitive difficulties associated with anticancer treatments. These techniques have illustrated exploratory and innovative notions such as 'personal cognitive reserve', 'individual biological profile of resistance to stress' and 'compensatory cognitive mechanisms'.

New Markers and Future Directions

New biological markers derived from translational research centered on the underlying mechanisms of chemo brain are needed for a better definition of this highly evolving concept. Future directions and areas of research are particularly brightly explored by Miller et al.[67] They discuss the relevance of future studies identifying psychological and genetic profiles of risk and the contribution of *IL-6* gene in behavioral pathologies in cancer patients and the demonstrated role of serotonin transporter polymorphisms in the relationship between stress and behavior alterations.[68,69] The need to develop prospective longitudinal assessments of both behavior and relevant inflammatory biomarkers in cancer patients is highlighted. Associations between IL-6 and CRP and depression, fatigue and cognitive dysfunction in cancer patients are also discussed, these 2 markers being the most reliable.[70-75] Hopefully, ongoing research into the mechanisms underlying these side effects of chemotherapy will form the basis of future interventional studies. According to Miller et al, 'cytokine antagonists, anti-inflammatory agents and drugs that disrupt cytokine-signaling pathways (e.g., NFκB and p38 MAPK) could target the most upstream elements in the cytokine-to-CNS-to-behavior cascade'. These authors propose also to target 'cortisol releasing hormone (CRH) pathway'. They also propose to develop 'new treatments supporting neuronal integrity/plasticity (neuroprotective agents) including drugs that stimulate the activity or signaling of relevant growth factors (e.g., BDNF)'.[76,77]

Conclusion

On the basis of recent findings from controlled prospective studies, it seems reasonable to advise breast cancer patients that approximately one-third of women receiving standard dose adjuvant chemotherapy experience very subtle disturbances in cognition, especially working memory, during and shortly following treatment but that, by 1 year after completion of treatment, cognitive function is not likely to differ from that of women receiving adjuvant hormonal therapy only.[18] It remains for future studies to address whether or not hormonal agents themselves cause cognitive side effects, as suggested by the same authors in another report, the course of those cognitive changes and whether or not they resolve with termination of treatment.[32]

Investigation of cognitive impairment associated with chemotherapy is an important area of research that presents methodological challenges. Those conducting such research should learn from the experience of diagnosing similar cognitive impairment in other populations (HIV,

multiple sclerosis) and adopt those methods most suitable for cancer patients. Well designed, with a proper hypothesis, randomized, longitudinal studies with an effective and sensitive method to measure MCI are needed. The use of the latest imaging techniques (PET, functional MRI) is a potential powerful tool. Results from previous studies show that sensitive cancer specific measures for the assessment of self-perceived cognitive deficits in different cognitive domains are required and emphasize the need for psychosocial counseling and support during treatment phase and follow-up care as well. Eventually, a better understanding of physiopathology will assist in the development of rational, targeted therapeutic options (e.g., cytokine antagonists or neuroprotectants) in the future.

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Chapter 13

Evaluation of Multiple Neurotoxic Outcomes in Cancer Chemotherapy

Bernard Weiss*

Abstract

Although it is now clear that cognitive dysfunction is a common accompaniment of cancer chemotherapy, its implications await further research and direction. Most of the clinical research relies on standard neuropsychological tests that were developed to diagnose stable traits. Cognitive dysfunction in patients undergoing treatment varies with time, however. Its dimensions will vary during the course of treatment, which generally consists of cycles of drug administration followed by recovery periods. To effectively determine the connection between chemotherapy and cognitive function requires neuropsychological tests based on performance, so that they can be administered repeatedly at specified times during the entire course of treatment and beyond. A number of computerized test batteries, many of which have been developed for environmental neurotoxicology, are now available that fit such criteria. Moreover, cognitive impairment is only one aspect of chemotherapy-induced neurotoxicity. A full appreciation of its scope requires assessment of sensory functions such as vision, audition and somatosensory properties and assessment of motor function. A program of research based on animal models is also essential. Only with animal models is it possible to determine dose-response relationships and to couple behavioral with mechanistic indices such as neuroplasticity. Animal behavior models play a vital role in environmental toxicology because, from them, it is possible to derive some index of exposure that limits adverse effects. However, as in human testing, it is critical to choose situations whose properties remain stable over long periods of time so as to trace the time course of neurotoxicity. Schedule-controlled operant behavior offers the most promising source of animal models.

Introduction

Oncologists are now aware that cancer chemotherapy can exert subtle as well as blatant neurotoxicity. The latter has been recognized even from the earliest days of chemotherapeutics and certainly in the case of radiation therapy. Gross sensory loss, such as deafness and evidence of abnormal central nervous system function such as seizures are inarguable. The less obvious outcomes, labeled as *chemo brain* or *chemo fog* by cancer patients, achieved far less clinical recognition because they came in the form of subjective complaints. The labels describe a syndrome characterized by memory difficulties, episodes of disorientation, inability to concentrate and other aspects of cognitive impairment. A T-shirt sold in the gift shop at the University of Rochester Medical Center reflects how keenly patients are aware of their difficulties. It is inscribed with one patient's view: "I have chemo brain; what's your excuse?" It reflects a situation that should cause us to ponder the limitations of and constraints imposed upon clinical medicine and cancer chemotherapy.

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Within the past decade, but especially quite recently, the application of neuropsychological test methods and their consistent findings has conferred scientific credibility on such patient reports.[1-4] The proportion of treated patients who may suffer neural damage due to chemotherapy is unknown, but longitudinal imaging studies on breast cancer patients treated with chemotherapy have indicated that white matter changes in the Central Nervous System are detectable in up to 70% of patients.[5] Other imaging studies also have shown enduring deficits. For example, data based on PET scans[6] showed altered activity in frontal cortex, cerebellum and basal ganglia in breast cancer survivors 5-10 years after treatment. And inagaki et al[7] found, by MRI, diminished volumes of gray and white matter in treated survivors one year after adjuvant chemotherapy for breast cancer.

Oncologists were not surprised to find that patients undergoing the rigors of chemotherapy experienced a multitude of side effects. Given the biological potency of these chemicals and the awareness that they damaged tissues other than those targeted by therapy, it seemed reasonable that patients would present a variety of complaints, some of which might be correlated with biological indicators such as anemia. Cognitive impairment might be seen as a relatively minor, vague and reversible component of such effects, as would fatigue and anxiety. How was the clinician expected to weigh such elusive functional deficits against the prospect that chemotherapy may prolong the patient's life? It was only after the launching of studies based on established neuropsychological tests that the extent and nature of cognitive impairment gained appreciation. These studies also indicated that such adverse effects continued long after therapy ended.

These newer findings are leading oncologists to consider more seriously the full extent of neurotoxic complications stemming from chemotherapy. Schiff and Wen[8] communicated their views in this way: "The CNS is an organ with a unique profile of vulnerability to antineoplastic treatments. In many cases, CNS neurotoxicity is the dose-limiting side effect of treatment for systemic and CNS neoplasms. Novel methods of delivering radiation and chemotherapy agents have led to recognition of new forms of CNS neurotoxicity."

Moreover, cancer has become a chronic illness and the number of long-term cancer survivors with neurobehavioral deficits will continue to increase. Cognitive impairment, furthermore, is only one component of chemotherapy-induced neurotoxicity, whose scope also embraces sensory systems (vision, somesthesis, audition, taste and smell), motor function (strength, endurance, coordination) and mood. Often, by the time neurotoxicity is apparent clinically, it has advanced to an irreversible stage. Sensitive tests can detect incipient impairment and forestall more serious conditions, but, especially for new drugs or drug regimens, oncologists do not know what to look for and may fail to detect the early, emerging indications of neurotoxicity. And, as some commentators have noted, the anxieties and health effects themselves provoked by cancer make it difficult to disentangle them from the neurotoxic effects of chemotherapy. Contrast this with the situation oncologists are familiar with in the case of anthracyclines, which present the risk of cardiac damage. Detection of cardiac damage at the point of imminent heart failure is too late to impede progression of the disease. Therefore, in an attempt to prevent anthracycline-induced cardiomyopathy, a number of surveillance methods have been used to try to detect problems at an earlier stage of chemotherapy. An equivalent rationale should be applied to neurotoxicity. Duffner[9] views this as an urgent need, noting that the mass of evidence indicating brain damage arising from chemotherapy is a "wake-up call to neuro-oncologists."

One reason for an emphasis on early detection is new information about how certain chemotherapy drugs act on the nervous system. A pioneering paper[10] revealed that the neurotoxic potency of three common chemotherapeutic drugs (carmustine (BCNU)), cisplatin and cytosine arabinoside (cytarabine) equaled or exceeded their potency as antitumor agents. When applied to cultured cells at what were calculated to be clinically relevant exposure levels, they proved more toxic for the progenitor cells of the CNS and for nondividing oligodendrocytes than for the cancer cell lines studied. When administered systemically in mice, these agents were also associated with increased cell death and decreased cell division in the subventricular zone, in the dentate gyrus of the hippocampus and in the corpus callosum. Some of these effects persisted for weeks after drug

administration ended. As they noted, "Our studies have multiple implications for future strategies of cancer treatment ... it seems that [doses of] chemotherapeutic agents sufficient to harm cancer cells may also damage many cell populations of the CNS ... It is also possible, however, that our results actually understate the extent of damage that occurs in association with chemotherapy."

These startling results underscore how little we really know about the neurotoxic consequences of cancer chemotherapy, a point emphasized by Noble et al (in press) in their review of chemotherapy-induced neurotoxicity. In fact, they point out that such effects are so widespread, because of the numbers of treated patients that, in essence, they are equivalent in scope to a major neurological disease. In support of their contention, they cite the breadth of data we now possess about the underlying pathological processes.

At this point, the scientific position of chemotherapy-induced neurotoxicity in oncology stands at about where environmental neurotoxicity stood over three decades ago.[11] Since then, it has generated a torrent of books, articles and conferences. It has turned environmental neurotoxicology into a science with multiple dimensions ranging from molecular mechanisms to animal models to epidemiology, all of which are waiting, as it were, to be applied to oncology. Questions about environmental chemicals have also enlisted both clinical neurology and neuroscience in determining the health risks posed by exposures.

Why haven't more features of this established scientific technology been applied to the neurotoxic risks of cancer chemotherapy? Shouldn't it be even more important now than in the past to adopt the most effective and precise scientific practices for the evaluation, prediction and prevention of neurotoxic outcomes? Wefel et al[12] have presented a cogent argument for such adoption: "Cancer is becoming a chronic illness, requiring on-going symptom assessment and intervention. The number of long-term cancer survivors will continue to increase as will the number of survivors with neurocognitive and/or neurobehavioural impairment."

Two Contrasting Views of Neurotoxicity

Environmental Neurotoxicology was propelled by legislation and regulation. Although the Toxic Substances Control Act (TSCA) was finally signed into law in 1976, its roots lay in the growing recognition that we were being exposed to thousands of synthetic chemicals as well as to industrial sources of metals that could threaten public health. The Council on Environmental Quality (CEQ) had issued a statement of concern in 1971: "The environmental effects of most of the substances discussed in this report are not well understood. Testing has largely been confined to their acute effects and knowledge of the chronic, long-term effects, such as genetic mutation, is inadequate. Although far from complete, available data indicate the potential or actual danger of a number of these substances." And even earlier, The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), passed in 1947, had governed the regulation of pesticides in the United States, a responsibility enlarged by the 1988 amendments that required pesticide reregistration and that prescribed a Scientific Advisory Panel to oversee the process, particularly from the standpoint of safety. Although both acts require that regulations weigh economic and other benefits against health risks, the latter demanded a process by which those risks could be quantified. Once quantified, exposure standards could then be prescribed that offered a stated degree of risk. Typically, because exposures to environmental chemicals offer no health benefits, the health risks assume priority and exposure standards are sought that offer a robust margin of safety.

Oncologists face a contrasting situation and history. In their universe, the sources of the health risks lie in the cancer itself. Therapy is administered to eliminate or arrest the cancer. Dose is determined by therapeutic effectiveness and side effects play a secondary role. One constellation of side effects, however, neurotoxicity, has proven to be especially troublesome. The reasons are not difficult to grasp. Subtle cognitive problems, such as memory loss, are often subjective and not easily evaluated in a clinical setting. How is the clinician expected to weigh such elusive functional deficits against the prospect that chemotherapy may prolong the patient's life? But what if, as noted by Dietrich et al[10] and emphasized by Ahles and Saykin,[3] the neurotoxic potency of certain treatment options exceeds their antitumor potency?

An appraisal of the current literature on chemotherapy-induced neurotoxicity reveals that it is guided primarily by an unstructured, informal clinical approach to some form of neurotoxic risk assessment. The term risk assessment generally denotes an approach that seeks early, or low-dose indices of adverse effects in an effort to prescribe exposure standards with a high enough margin of safety to escape even minimal effects. In this form, it is not applicable to chemotherapy. Under a less constrained definition, however, it would describe a process in which detection of adverse effects, by sensitive methods, would lead to a re-evaluation of a patient's regimen.

In practice, clinical oncologists become aware, sometimes because of patient complaints, that certain courses of treatment are inducing some form of neurotoxicity; for example, trouble hearing. Or, investigators pursuing research on chemotherapeutic actions and effectiveness uncover clinically significant neurotoxic effects. They may then ask about the scope and character of such effects, but not in a quantitative sense. Generally, they do not engage in a prolonged or extensive search for the time or dose levels at which adverse effects begin to emerge, nor for how long after the course of treatment they persist. Although these are crucial questions for evaluating patient quality of life and the benefit-risk balance and can be determined if the proper instruments are applied, they still mostly remain as background issues.

This chapter describes how the kinds of standards, methods and approaches that have informed progress in environmental neurotoxicology can lead to procedures and techniques that could be applicable, with modification, to the ways in which we evaluate neurotoxic potential and outcomes stemming from chemotherapy. In essence, neurotoxicity assessment can be seen to include three functions. One is simply to insure clinical awareness of the patient's state. Another is to conduct what in environmental toxicology would be a risk-benefit analysis. Third is to build a database. Here, we would use advanced assessment techniques, especially for sensory and motor function that lie outside the scope of conventional neuropsychological tests.

In parallel, especially for exploring new therapies, it is crucial that they be evaluated in animal models for neurotoxic potential before they are applied to patients. Although new drugs follow a series of tests for adverse effects before they are administered to humans, the kinds of neurotoxicity of concern to oncologists are not specifically included. A model for such assessments will be described in this chapter.

Dimensions of Neurotoxicity

Cognitive impairment is only one component of neurotoxicity, whose expression also embraces sensory systems, motor function and mood and personality disorders. Sensory system damage and dysfunction arising from chemotherapy have been noted for vision, somesthesis, audition and olfaction. Generally, when reported, they have advanced to a clinically detectable stage and have not been studied to determine at what point function begins to show evidence of impairment. Motor function, except for weakness, has received even less attention. The main lesson we have learned from research on cognitive function is one that neurotoxicolgists learned long ago in their studies of exposed populations such as workers. Namely, that even during the stage of what might be called silent or incipient neurotoxicity, before patients became aware of deficient function, sensitive neurobehavioral tests would have detected impairment and provided clinicians with information that might have forestalled more serious conditions.

Lessons Learned from Studies of Cognitive Dysfunction

Investigations of cognitive dysfunction in chemotherapy were not the product of attempts to set exposure standards, or of the appearance of overt neurotoxic signs such as seizures but, instead, complaints by patients. These complaints drove chemotherapy research in an unaccustomed direction; namely, validation of subjective adverse effects. It is informative to review this history.

Oncologists were not surprised to find that patients undergoing the rigors of chemotherapy experienced a multitude of side effects. Given the biological potency of these chemicals and the awareness that they damaged tissues other than those targeted by therapy, it seemed reasonable that patients would present a variety of complaints, some of which might be correlated with biological

indicators such as anemia. Cognitive impairment might be seen as a relatively minor, vague and reversible component of such effects, as would fatigue and anxiety. It was only after the launching of studies based on established neuropsychological tests that the extent and nature of cognitive impairment gained appreciation. These studies also indicated that such adverse effects continued long after therapy ended.

Several reviews of these findings have now appeared.[1-3] Although many of the studies reviewed were based on small samples and although in total they reflect some inconsistencies, the weight of evidence points to effects that in many patients persist for years beyond the termination of treatment. The reviews also agree on the importance of longitudinal prospective studies, on the need for more research on potential mechanisms, on the need for more standardization and perhaps greater breadth of neuropsychological tools and approaches and the critical role of animal studies to clarify both the scope and mechanisms of impairment.

This literature, although firmly establishing the objective basis of patient reports, is still largely confined to the narrow question of cognitive dysfunction.

This chapter maintains that oncologists and cancer researchers should enlarge their view of what constitutes neurotoxicity and how to measure and investigate it. I will adopt, as a means of framing my argument, the approach that would be relied on were chemotherapy viewed as equivalent to an environmental exposure. To do so I will discuss tools and approaches that can be used to trace the status of neurotoxic responses during and after a course of treatment. Optimally, these tools would be employed before chemotherapy begins and would be used to monitor patients on specified occasions during the course of chemotherapy and for some period afterward. Predictive assessments based on animal models will be discussed also.

Cognitive Function Approaches

Many of the earliest attempts to assess neurotoxicity in humans adopted procedures that had been developed for clinical neuropsychological testing. Such procedures often proved poorly designed for research in neurotoxicology because they evolved as diagnostic instruments, not as tools with which to screen populations or for experimental investigations. They typically were used to provide a functional profile of a patient, often one who had suffered brain damage. For example, they were designed to evaluate stroke patients, or those suffering from disorders such as schizophrenia. They had not been contrived to determine, for example, whether workers exposed to pesticides differed from controls on various psychological dimensions, or to yield a dose-response function for acute exposures relating concentration to performance. They most certainly were not devised to trace the development of adverse effects during a period of exposure to a potentially neurotoxic agent. Nevertheless, lacking more appropriate tools, they were invoked to respond to some pressing questions about exposed populations. The pioneering reports from the Finnish Institute of Occupational Health[13] relied heavily on clinical instruments. Neurotoxicology, however, also borrowed techniques from the experimental psychology laboratory. Such techniques lacked the standardization and norms provided by most clinical tests, but offered the virtue of greater specificity, flexibility and a scientific basis.

The current literature on cognitive impairment arising from chemotherapy is almost exclusively based on neuropsychological tests designed to assess a stable and enduring condition. Such tests are not equivalent to the tools required to assess patients repeatedly during treatment to determine whether and to what degree, they are impaired. The necessary tools, especially for measurement of cognitive function, have different properties. They measure performance.

Performance tests differ from conventional clinical tests in several respects.[14] Tests devised for clinical applications aim to differentiate between individuals and to offer or substantiate a diagnosis. Performance tests are designed to differentiate among stressors such as drugs, toxic chemicals and conditions such as sleep deprivation. Clinical tests should be relatively insensitive to environmental perturbations because they should serve to identify stable traits in the individual, but performance tests are expressly designed to reflect such perturbations. Finally, clinical tests generally are meant to be given only once.

In contrast, performance tests should be capable of repeated administration, as in monitoring changing response patterns over an experimental session, or in overseeing the status of workers in a particular environment where they are exposed chronically to presumed or suspected neurotoxicants and where they undergo repeated assessment. There is now a robust literature describing the kinds of instruments that show promise as assays of nervous system function for monitoring patients undergoing chemotherapy or in following the progression of neurodegenerative disorders such as Alzheimer disease and Parkinson disease. Chemo brain assessments, either for research or for patient evaluations, should be based on performance tests. The primary question in both instances is how function changes over time.

Moreover, the time taken for evaluation may be limited, especially in the workplace, so that a compact but comprehensive test battery is more suitable than the typical, largely paper and pencil tests administered by clinical neuropsychologists. Responses on paper and pencil tasks also have to be scored and transcribed, leading to transcription errors and rescoring.

Faced with the need to assess specified populations exposed to defined hazards, or to evaluate particular stressors experimentally, neurotoxicology turned to the development and adoption of computerized testing. It made the mechanics of testing more efficient; it offered considerably more uniformity in how test stimuli were presented; it made it possible to test several subjects simultaneously; it could use testers who did not require advanced clinical training; it could automate scoring and analysis; it allowed remote testing (as in an exposure chamber); and it proved adaptable for translation of procedures used in the animal laboratory. Perhaps most important of all, it moved human testing from clinical diagnosis to the realm of performance.

Slikker et al[15] offer a comprehensive discussion of the properties and usefulness of computerized test batteries and how they reflect and extend traditional approaches. Several current batteries have been used widely enough and are well-enough established, to be considered as appropriate instruments for neurotoxicology. The CANTAB[16] consists of a suite of computerized tests, now numbering 22, that embrace a variety of cognitive functions: visual memory, executive function, working memory, semantic and verbal memory, attention, decision making and response control (designed to assess behaviours such as impulsivity). Most of the tests are explicity designed to be independent of language and culture. Alternate forms are available for repeated testing. The CANTAB has been used extensively in patients with Alzheimer and Parkinson disease. The BARS (Behavioural Assessment and Research System) battery is specifically designed for the detection of neurotoxicity in populations with limited education or literacy.[17] It too can be used for repeated assessments.

One of the newer features of computer-based testing is the incorporation of instructional materials. Particularly because of the variety of populations that undergo assessment for neurobehavioural function, including those unfamiliar with testing procedures and that are often illiterate, more effective means for communicating test instructions have been sought by investigators. The computer itself is a tool that can be adapted for such a purpose. Rohlman et al[18] in response to such a need, use computer graphics for the BARS battery to teach subjects how to perform the tests before the test items themselves are presented. The technique relies on a sequence of approximations to the final performance, much like the technique, called shaping, used to train animals on schedule-controlled operant behaviour.

A useful illustration of current technology for neurobehavioral testing is the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB is a computer administered battery consisting of 14 individual neuropsychological tests (see Table 1). The subtests are designed to measure cognitive abilities reliant on frontal/subcortical circuits and has been used extensively in research on these abilities in nonhuman primates and in humans with Parkinson and Huntington disease. Included in the CANTAB battery are measures of working memory and cognitive flexibility. Performance on these CANTAB subtests is sensitive to early deficits in un-medicated PD patients. The CANTAB tests have also been used in studies of toxic and metabolic disorders, effects of substance abuse and evaluation of neurotransmitter modulation in normal controls and disease. The CANTAB has been used extensively in patients with Alzheimer and Parkinson diseases.[19] The CANTAB is well suited for use in neurotoxicology.[16]

Table 1. CANTAB subtests and abilities assessed

CANTAB Subtest	Ability Assessed
Motor Screening	Visual, movement and comprehension difficulties
Big/Little Circle	Concept formation, learning and reversal
Delayed Match to Sample	Immediate and delayed perceptual matching
Intra-Extra Dimensional Set Shifting	Rule acquisition and cognitive flexibility
Matching to Sample Visual Search	Ability to match visual samples and measures reaction and movement time
Paired Associates Learning	Episodic memory and learning
Pattern Recognition Memory	Recognition memory for patterns
Reaction Time	Speed of manual response
Rapid Visual Information Processing	Sustained visual attention
Stockings of Cambridge	Spatial planning and motor control
Spatial Recognition Memory	Recognition memory for spatial locations
Spatial Span	Working memory capacity
Spatial Working Memory	Working memory and strategy use
Verbal Recognition Memory	Immediate free recall and immediate and delayed recognition memory

The CANTAB tests have excellent face validity for the constructs measured. Each test was developed from established animal behavior paradigms and validated in patients with damage in specific areas of the brain including frontal and temporal lobe and basal ganglia. In addition, many of the sub-tests (Spatial Span, Spatial Working Memory, IDED Set Shifting; Rapid Visual Information Processing; Paired Associative Learning) have been studied with functional neuroimaging to provide confirmation of the neuro-anatomical substrates supporting each test.

Sensory Function

Vision

Visual system toxicity induced by anticancer chemotherapy is not uncommon and has been recognized from the beginning. A statement by Schmid et al,[20] however, points up the discrepancies between what constitutes neurotoxicity by clinical criteria and the criteria that would be used in environmental risk assessment (my italics):

"Many ophthalmic complications have been reported for these new cytotoxic chemotherapeutics, some of which are reversible if detected early enough ... *At first, many of these ocular toxicities are hardly detected* ... However, these side effects may turn out to be irreversible by the time the symptoms are recognized." Among the functional complaints listed by Schmid et al (2006), which could be classified as early indications of potential damage, are blurred vision, decreased color vision, diminished visual acuity, diplopia, night blindness, photopsia and photophobia. As they note, "The possible reversal of some of these side effects, *if discovered in time*, emphasizes the need for clinicians to be aware of these ocular reactions and suggests an immediate consultation with an ophthalmologist."

Is referral for consultation, after a patient complains, an adequate response? Both vision scientists and neurotoxicologists who employ measures of visual function as an index of adverse effects, would

not see it as adequate. Tamoxifen offers an instructive example. Eisner and Incognito[21] undertook a comparison of two groups of middle-aged women 40-69 years of age, as a follow-up to previous work on color vision abnormalities and chemotherapy. One group had been using tamoxifen, both as adjuvant therapy after successful treatment for early-stage breast cancer. They comprised two subgroups, one on medication for over two years, the other treated for less than two years. The controls were not using any hormonally-acting drugs. Relying on a color-naming psychophysical procedure, they found that tamoxifen treatment produced a tendency to label test stimuli of 440 nm, typically called "lavender," as "white." This is the kind of subtle functional change that tends to precede clinically evident toxicity.

Although the precise control of wavelength by instrumentation used by Eisner and Incognito[21] would be confined to only a few institutions, other means for measuring color discrimination are available. The Farnsworth Munsell 100 Hue Test presents the patient with four trays containing a total of 85 removable color reference caps spanning the visible spectrum in small increments of hue. Color vision abnormalities are assessed by the ability of the patient to arrange the color caps in order of hue. A briefer version, using only 15 color tiles (the FM D-15) is also used, while another brief version, the Lanthony D-15, uses desaturated colors to separate "normal" color perception from the kind of subtle color deficiency that may accompany workplace exposures to substances such as organic solvents.[22]

In some reports, blurring of vision has been noted as a patient complaint or observation, but not followed up with appropriate tests. The typical Snellen eye chart used to measure visual acuity presents the patient with a high-contrast target, namely, black letters on a white background.

Contrast, however, is an important visual parameter because when we direct our vision to a scene, objects and their surroundings vary in contrast. This kind of pattern vision is explored by vision scientists by displaying what in essence are alternating dark and light bars, or gratings, that are characterized mathematically by their width (or spatial frequency). Charts containing gratings of varying spatial frequency, contrast and orientation can be used to assess contrast sensitivity and are commercially available. In addition, simpler charts are available that have transformed these parameters into a display of letters on a background. Blurring represents a loss of contrast sensitivity. The tools noted above for assessing contrast sensitivity have shown effects from exposure to chemicals such as methylmercury, acrylamide and volatile organic solvents. They have also detected visual system impairment in patients with Parkinson disease and multiple sclerosis. They can be used as a relatively quick and simple assay for incipient visual dysfunction of the kind that, unlike conventional visual acuity measures, cannot be corrected with glasses.

Portable charts for this purpose are available. The Pelli-Robson and Mars tests use a single large letter size with contrast varying across groups of letters.[23] The Pelli-Robson chart uses letters (6 per line), arranged in groups whose contrast varies from high to low. The Mars test is similar. A more elaborate test, the Functional Acuity Contrast Test uses sine-wave gratings, the standard for vision research, mounted on a chart. It was used by Schreiber et al.[24]

The National Eye Institute (NEI) has devised a questionnaire that can be used for screening. The Visual Functioning Questionnaire—25 (VFQ-25) can be obtained from the NEI web site. Its core defect is that the more subtle indications of early-stage visual dysfunction escape subjective assessment and detection.

Hearing

The auditory system is vulnerable to many chemical exposures. Drugs such as the aminoglycosides and workplace compounds are examples. Among chemotherapeutic agents, cisplatin is notorious for its ototoxicity. Perhaps as many as 40% of patients report hearing difficulties. As always, because it is so effective a drug against conditions such as testicular cancer, oncologists are reluctant to reduce dosage even when hearing tests indicate that the patient is suffering auditory system damage. Dosage reduction, however, may not be the only alternative. Rademaker-Lakhai et al[25] carried out an audiometric study comparing different dosing schedules of cisplatin. They found that hearing impairment was more severe for the schedule administered the every 2 weeks versus every week when the dose levels

with the same dose-intensity were compared. If dosing schedule can be altered without reducing the effectiveness of chemotherapy, then patients can benefit if audition is evaluated during the course of therapy and treatment protocols changed to reduce toxicity.

Such flexibility depends on access to audiometric facilities. For those clinical settings wishing to monitor hearing function, it is vital to note that some superficially simple procedures may provide misleading results. A core problem with ototoxicity in chemotherapy is that the National Cancer Institute's reporting system, Common Terminology Criteria for Adverse Events, or CTCAE does not consider high-frequency hearing loss (above say, 8,000 Hz). Such losses are the first indication of auditory system damage. The frequencies important for vocal communication are significantly lower, so that ordinary patient interviews, such as the Hearing Handicap Inventory in the Elderly, from the Surgeon General. Conventional audiograms will fail to detect the early signs of hearing loss because they typically do not assay frequencies above 4,000 Hz. Tests beyond conventional audiometry such as otoacoustic emissions (OAEs) and evoked potentials (e.g., brainstem auditory evoked responses, or BAERs) make it possible to detect auditory damage at an early stage.

Somatosensory Function

Some observers contend that the most disabling form of chemotherapy-induced neurotoxicity is peripheral neuropathy. Cavaletti et al[26] noted that it could be the side effect of treatment most likely to elicit a reduction of dose. Postma et al,[27] relying on a questionnaire survey, believe that the incidence may be as high as 100%. Rating scales, such as the Total Neuropathy Scale (TNS), are useful for assessing symptoms, but their ability to quantify dysfunction is limited. At the same time, the instruments available for quantification have their own limitations. The vibrating probes used by devices such as the Bioesthesiometer deform the skin according to the amount of pressure exerted by the tester, so that crucial variable is essentially uncontrolled. Maurrisen and Weiss[28] describe the problems with instruments of that design.

Tactile sensitivity can be addressed by fairly simple devices, however, provided the procedures are conducted according to established psychophysical principles. Examples can be seen in Tremblay et al,[29] who directed their study at how age affects tactile sensitivity. The authors used three different tests to measure sensitivity in the right index finger. One was used to determine pressure sensitivity. Skin indentations were produced by applying a set of Semmes—Weinstein nylon monofilaments to the finger. The actual force is scaled approximately logarithmically in mg (but psychophysically it provides a linear scale of perceived intensity). Each filament was applied to the finger in a sequence of increasing perceptual difficulty for one second. However, each trial consisted of a temporal forced-choice decision in which subjects were presented with two time periods, one containing the stimulus (monofilament applied) and one containing no stimulus. Subjects were asked during which period the stimulus was applied. Sensitivity thresholds were calculated by determining which monofilament gave the lowest buckling force at a detection rate of 75%.

Spatial acuity was tested by measuring gap detection. A series of 14 small square-shaped blocks made of high-density Styrofoam were precision milled so that one of the sides contained a gap of specific dimensions while the other side was left intact. The subjects were asked to report which side of the block contained the gap when the experimenter pressed the block against the finger. By using a range of gap widths and a two-alternative forced-choice procedure, the investigators were able to calculate a gap threshold. The third test, thickness discrimination, consisted of presenting the subject with a set of 12 square Styrofoam plates of differing thickness grasped between the thumb and forefinger. As in the other tests, a standard, 5 mm thickness was compared with a different plate in a two-alternative forced-choice procedure.

For all three procedures, the younger group of subjects (mean age 23 years) were markedly more sensitive than the older group (mean age 70 years). On the basis of these differences, these procedures should prove useful for assessing losses of mechanoreceptor sensitivity due to peripheral neuropathy. Measures of two-point threshold, often determined with calipers, could also prove useful, but the variability introduced by examiner differences in applied pressure can be problematic.

Olfactory Discrimination

Diminished smell acuity is widely recognized as an accompaniment of chemotherapy.[30] A simple way to test olfactory function, used in studies of Parkinson disease and Alzheimer disease as well as for workers[31] makes use of the University of Pennsylvania Smell Identification Test (UPSIT). It is a 40-item test and consists of 40 odorants in 4 booklets containing microencapsulated odorants that are released by scratching standardized odor-impregnated test booklets. The score is number of errors. It is the most widely used instrument for assessing smell loss and has become the standard for such assessments.

Motor Function

Most comprehensive neuropsychological test batteries used in environmental neurotoxicology, particularly those based on computer presentation, include some form of motor function assessment. Because cancer patients undergoing chemotherapy frequently report loss of strength, slowing of movement and reactions and problems with coordination, motor function testing would be an essential component of any test battery aimed at monitoring adverse neurobehavioral effects during and after treatment.

Finger-tapping rate is a common measure. It requires the subject to tap a specific key on the keyboard as rapidly as possible in a 30-second period and has been used in studies of mercury vapor[32] and manganese exposure. The BARS test battery uses a special, simplified keyboard for this purpose.[18] The Grooved Pegboard consists of a small board containing a 5 × 5 set of slotted holes angled in different directions and 25 pegs with a ridge along one side, requiring the peg to be rotated into position for correct insertion. This is a test of fine manipulative dexterity and motor speed. The completion time in seconds is recorded for each hand. It has been used in studies of lead neurotoxicity[33] and mercury vapor.[32] More advanced assessment methods are also available; they were designed for situations in which the predominant questions arose from motor effects. For example, Wastensson et al[34] employed a system that measured the speed of rapid alternating pointing movements between two targets and one used to quantify the performance of rapid alternating movements of the forearms.

Animal Models

Purpose of Animal Models

In their reviews of cognitive dysfunction associated with chemotherapy, Tannock et al[35] and Ahles and Saykin,[3] among others, emphasized the need for animal models both to identify the scope of possible adverse responses and to relate them to mechanistic measures. Hardly more than a handful of current publications have attempted to address such questions. Examples include: Lee et al,[36] (young and old female rats administered 5-FU or cyclophosphamide and studied with the Morris maze or Stone maze); Seigers et al,[37] (rats administered methotrexate and studied with Morris maze and novel object recognition tasks); Foley et al,[38] (mice treated with either methotrexate or 5-FU, studied for lever-press acquisition); Konat et al,[39] (combination of adriamycin and cyclophosphamide in rats and studied with passive avoidance); Mustafa et al,[40] (rats administered 5-FU and studied with object location recognition); Winocur et al,[41] (mice administered a combination of methotrexate and 5-FU and tested with different Morris maze tasks). Although such studies have provided much useful data, overall they lack cogency as models for clinical extrapolation for four reasons: first, they tend to rely on methods that typically are applied only once, while chemotherapy regimens generally administer drugs as a series of treatments or cycles. The basic need is for methods capable of monitoring the entire course of treatment as well as the persistence of neurotoxic effects following treatment. Second, most tend to study only a single endpoint while adverse effects in the clinic include multiple endpoints. Third, some typically assess only single drugs, while clinical practice dictates drug combinations. And, If they study combinations, they rarely assay the individual components in depth. Fourth, they offer rather limited dose-response information, tending to choose a single dose or dose combination on the basis of other toxicity

information, previous literature, clinical values, etc. Dose-response information provides a basis for mechanistic exploration.

Animal models are needed that are capable of tracing the onset, time course and persistence of neurotoxicity—the key clinical questions.

Procedures

Appropriate procedures would be built around endpoints that are assessed repeatedly during courses of treatment designed to mimic clinical practice. For example, they might compare a widely-used drug combination with its components. And, following the scheme by which environmental chemical exposure standards are derived, they would explore dose-response functions.

The ultimate aim of animal models would be to lay the foundation for preclinical assessments capable of predicting the neurotoxic profile of various chemotherapy regimens. Such tools, ultimately, would have the potential to be translated into a comprehensive test battery for monitoring patients. The parallel aim would be to provide a test bed, so to speak, for mechanistic research such as that of Dietrich et al[10] and Han et al.[42]

In essence, then, animal models would begin to initiate the development of a suite of preclinical assessments that (1) can be used to predict the neurobehavioral outcomes of individual chemotherapy agents and of multi-drug chemotherapy regimens; (2) can be used in situations requiring reliable, efficient screening for new treatment regimens; (3) can be translated into procedures for monitoring patients; (4) can be used to predict or monitor the usefulness of countermeasures aimed at reducing the neurotoxic effects of chemotherapy. Preclinical assessments would be especially useful in this latter context because cancer treatments are almost never given at the optimal dosages or schedules to kill cancer cells. Instead, treatment choices tend to be governed by the need to limit toxicity, which often takes the form of neurotoxicity.

Choice of Doses

Identifying neurotoxicity is not a challenging problem. Even the crudest observational screens are capable of doing so. Useful animal models would include, at some stage treatment protocols congruent with clinical practice. In particular, they would build on the fact that chemotherapy is typically administered for several courses in a series of cycles, with each period of treatment followed by a rest period. Furthermore, because it has been recognized for nearly 30 years that adjuvant polychemotherapy is superior to single-agent strategies (cf., ref. 43), they would assess combinations as well as single agent regimens. For example, a widely-used combination given for adjuvant breast cancer therapy is CMF, or the combination of cyclophosphamide, methotrexate and 5-fluorouracil. As noted by McArthur and Hudis[43] it is a particularly reasonable option for patients who have lower-risk tumors and It is also an attractive combination for evaluating animal models because it has been shown to produce cognitive impairment in about 50% of treated patients.[44-46]

Only after many environmental neurotoxicants had been studied individually (e.g., lead, methylmercury, PCBs) did investigators begin to consider animal models for the assessment of mixtures. In the current literature on animal models for cancer drugs, when combinations are studied, disentangling the contributions of the individual components to the effects of polychemotherapy regimens is rarely attempted even though it would offer oncologists some basis for decisions about balancing therapeutic effectiveness versus toxicity. A related problem is the lack of dose-response information. Dose-response methodology is critical for setting environmental exposure standards to protect public health. For chemotherapeutic drugs, the aim would be to correlate dose with the incidence and characteristics of adverse effects. Such properties would need to be determined before mixture studies are attempted.

The importance of dose-response information is underlined by the significant proportions of patients who experience effects such as nausea, vomiting, stomatitis, constipation, fatigue and other adverse symptoms. Because these are also the doses associated with impaired cognitive function, one approach to designing a useful animal model would be to use them as the anchors for dose-response calculations. For example, the clinical doses, in the form of conversion to doses for a rat model, might be considered the baseline (100%) doses. Doses equivalent to 50% and 25% of

the clinical dose as well as the control vehicle could then be used to choose an appropriate range of doses. Such a strategy might be used to disentangle side effects, such as nausea, from performance effects on neurobehavioral tests and to obtain less confounded, "purer," measures of neurotoxicity. Equally important, a dose-response function provides a basis for exploring the relationship between mechanistic measures and their expression in behavior.

As noted earlier, one defining feature of chemotherapy is treatment schedule. Treatments are generally given in cycles, with periods of recovery between treatments. Protocols for evaluating neurotoxicity have to take this feature into account when they are being designed. That is, they must be capable of application at least during the periods between treatments as well as for some duration of time after the course of treatment has ended so as to capture the kind of persistent, lingering effects seen in some patients and documented in rodent studies such as that of Han et al.[42]

Choice of Endpoints

An example of a protocol focused on cognitive performance provides an approach that would prove useful for other kinds of neurotoxicity such as those discussed by Weiss.[47] Cognitive complaints by patients were the main incentives for research into the more subtle neurotoxic manifestations of chemotherapy and remain so today.

Schedule-Controlled Operant Behavior

Stable behavioral baselines are required for any scheme aimed at monitoring adverse neurotoxic effects during the course of treatment. Schedule-controlled operant behavior is ideally suited for this role. It is widely used in psychopharmacology because it can be used to compare different drugs and acute doses against a stable criterion that allows repeated testing over extended periods of time (e.g., ref. 48). It is used extensively in environmental neurotoxicology because it can be used to trace changes over time with chronic exposure (e.g., ref. 49 and aging, ref. 50).

A typical experimental setting is a standard operant chamber with two levers and a device for delivering food pellets (Fig. 1). A prototypical situation is one in which a rat, by depressing one of the levers mounted on the front panel, can trigger the release of a small food pellet. The food pellet is termed a reinforcer and the process is termed reinforcement. The rat's responses produce food delivery according to the contingencies, or schedule, programmed by the experimenter. Typically, rats, say, are maintained at about 80% of free-feeding weight so that they will perform specified behaviors rewarded by pellet deliveries.

We use the term operant to refer to learned or acquired behavior that is controlled by its consequences. Most complex human behavior falls into this niche. The term, schedule-controlled, refers to the way in which experimenters define the relationship between a specified response by the organism and the effects of that response. The term schedule describes the relationship between the behavior and its consequences. For example, a fixed-ratio schedule of reinforcement defines a situation in which a specified number of responses, such as lever presses, is required for delivery of a food pellet reward.

Schedule contingencies come in many varieties. Some are based primarily on time. Interval schedules specify relationships between elapsed time and the availability of reinforcement. A fixed-interval schedule might specify that the first response 5 minutes since the last reinforcement will produce the next reinforcement (FI 5). Another way to construct a schedule based on elapsed time is to specify the interval between successive responses; a Differential Reinforcement of Low Rate schedule might require a minimum of 20 secs between responses (DRL 20) for reinforcement. Response number, in the form of ratio schedules, is another widely-used performance criterion. A fixed-ratio schedule might require 100 responses (FR 100) for reinforcement delivery.

The primary virtue of schedule-controlled operant behaviour is its flexibility. It can be used to study rate of responding during steady-state behaviour, or the acquisition of new behaviour against a background of stable behaviour, or the ability to distinguish related visual stimuli, or the speed of responding to a stimulus, or the accuracy and other characteristics of motor control.

One operant procedure that would serves as a useful example for such a project provides a measure of working memory and is termed Delayed Spatial Alternation. Of all the complaints

Figure 1. Standard operant chamber containing response levers, feeder (behind panel) and stimulus lights.

registered by chemotherapy patients, memory difficulties seem to be among the most frequent and distressing (cf., refs. 47,51). With this procedure, the rats are tested with a procedure depicted in Figure 2 (e.g., refs. 49,52,53). Here, the pellet rewards are delivered for pressing the lever (right or left) opposite the one that previously was designated as the correct one. That is, the correct lever alternates between sides. The memory component is assessed by interposing delays between choices, so that the rat has to remember which was correct on the previous choice. The delays will vary between 0.5 and 12.0 seconds; typically, the longer the delay, the less the accuracy. All delays are sampled during a 45-minute test session. Stable performance is typically achieved by 60 training sessions (12 weeks). With stable performance in place, we can then trace how it varies over the course of treatment; that is, the immediate after-effects of treatment, how much recovery occurs between treatments and how much impairment (if any) persists beyond that point.

Five different delays are presented within the same session. Generally speaking, the longer the delay, the more difficult it is to remember, with the result being a within session function showing more criterion responding at shorter delays than longer ones. Drugs that interfere with memory will shift the function, but overall responding itself will provide a confirmation of food motivation.

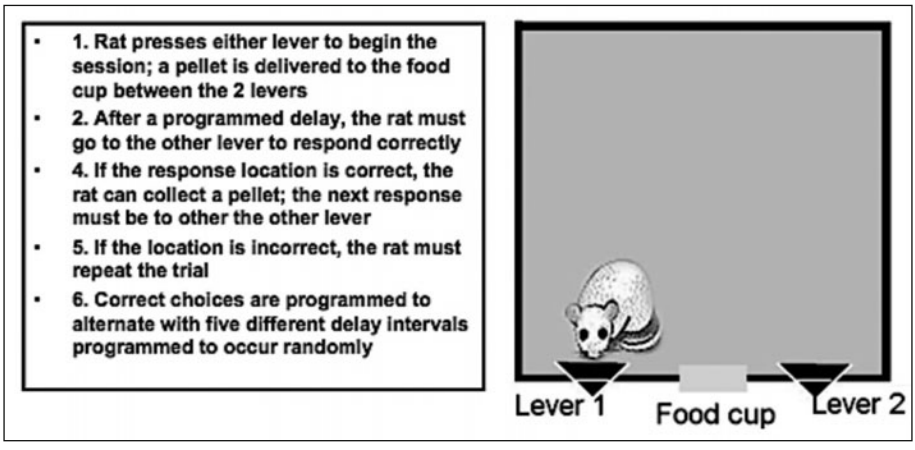

Figure 2. Schematic for Delayed Spatial Alternation.

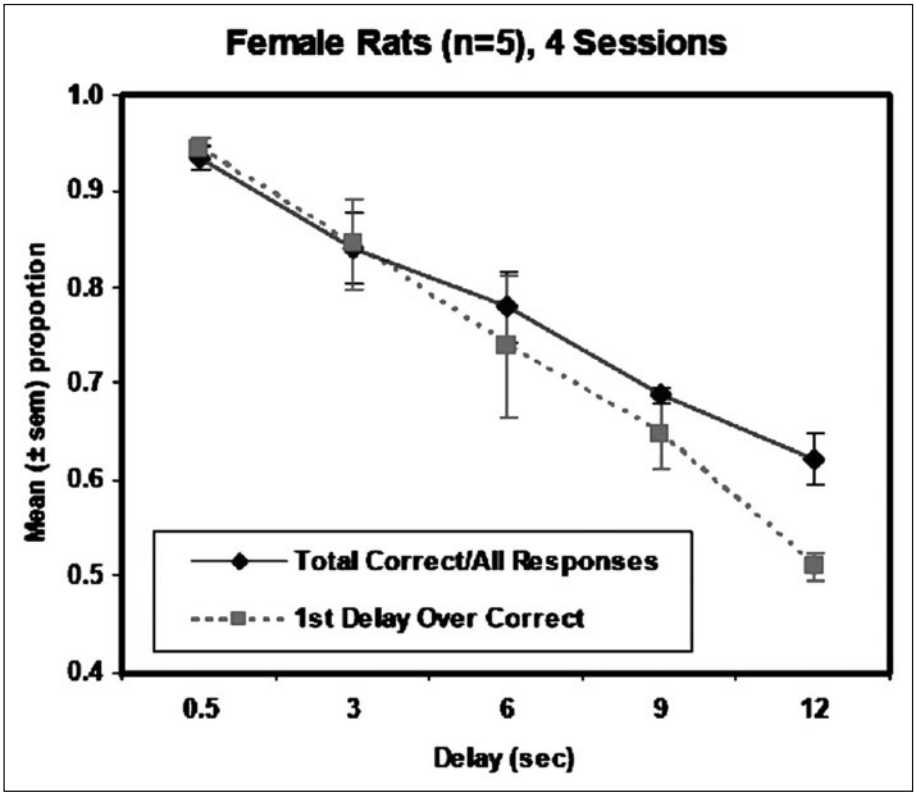

Figure 3. Performance of 5 trained female rats on a Delayed Spatial Alternation task. The delays ranged from 0.5 to 12 seconds. Both measures of performance, total correct and the first response following the delay, showed the expected decline in accuracy as delay duration increased.

Figure 3 presents the results of a study in female rats tested, after preliminary training, with delay values of 0.5, 3, 6, 9, 12-sec. These were presented randomly during a session, each for 40 times, for a total of 200 trials. The chart shows that the number of correct responses varied inversely with delay duration, as would be expected.

Alternative Approaches

Objections are sometimes raised about the resources required for these kinds of studies: that is, the lengthy training periods and the investment in equipment. We find it difficult to conceive of a complex learned behavior, stable over time, that does not require extensive training. Surely the cognitive functions that underlie the difficulties complained of by patients are products of a lifetime of experience, so we can hardly expect to predict such effects by using quick, simple behavioral indices. The equipment issue is easily resolved. If we aim to investigate and compare many different regimens as they become targets for evaluation, we need to be able to study substantial numbers of animals under standard conditions. One laboratory staff member can control and monitor 20 operant chambers per 1-hr session (as in our laboratory), or four 1-hour sessions per day, because of automation and have the results and even many statistical analyses processed automatically as well. It offers, compared to other approaches, what might be termed a high-throughput solution to testing potential treatment regimens. Procedures that superficially seem less demanding and expensive, such as the Morris maze, can be much more costly. Like similar methods, the water maze requires one staff member to test one animal at a time—a very expensive and time-consuming procedure. In addition, it is not a procedure that is appropriate for daily testing over a period of months. Further, we have found that staff members differ among themselves in how they handle animals and in their observational skills. This is another source of variability often overlooked.

Conclusion

This chapter is an attempt to provide a foundation for the evaluation of neurotoxicity evoked by cancer chemotherapy. Its outlook is framed by the experience of how to assess neurotoxic risks posed by environmental chemicals, a situation in which prevention of adverse effects predominates. It has emphasized behavioral testing rather than mechanistic studies because its target is a model for tracing the onset and persistence of neurotoxicity in patients. In accordance with this aim, it also includes an example of how preclinical assessment in animal models might be undertaken. Here, dose-response functions and stable performance baselines are critical, as they have been shown to be in the evaluation of environmental neurotoxicants.

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Chapter 14

Chemotherapy-Related Visual System Toxicity

Robert B. Raffa*

Abstract

Most, if not all, of the studies that report cognitive impairments in patients who have been treated with cancer chemotherapy also report deficits involving the visual system (e.g., visual-spatial function or visual memory). The visual system seems like a likely susceptible target of cytotoxic drugs. Therefore, some portion of the vision-related cognitive deficits of chemo fog/chemo brain might result from a direct action of the drugs or from site/site interaction between effects on the visual system and other critical brain regions. This chapter is a succint summary of a more expanded review.[1]

Introduction

In reviews of studies that report the results of testing of cancer patients who had received chemotherapy as part of their treatment, it is common to find deficits that are listed as 'visuo-spatial,'[2,3] 'visual-motor',[4] or 'visual memory'.[5] The extent to which chemotherapy-induced visual defects might contribute to the spectrum of chemo fog/chemo brain impairment is unknown, but is worthy of consideration.[6] It is incontrovertible that certain chemotherapeutic agents can produce toxic effects on the visual system. Whether or not the regimens of these agents that are used to treat cancer are sufficiently high or prolonged to produce toxicity sufficient to manifest as cognitive impairment is uncertain. However, even if not sufficient to cause frank cognitive impairment, visual impairment during testing might skew the results toward artificially large negative findings.

The possibility that chemotherapeutic drug-induced toxicity to the visual system might contribute—alone or synergistically with other toxicities—to some cognitive deficits described in chemo fog/chemo brain is briefly summarized.[6]

Visual-System Deficits in Chemo Fog/Chemo Brain

A review of early studies of adjuvant cancer chemotherapy-induced cognitive deficits finds several descriptions of impaired functioning that might actually be secondary manifestations of toxicity to the visual system (sensory input) rather than to direct effect or sole effect on cognitive functioning (processing).[1] These are briefly summarized in Table 1.[2-8]

These and other studies like them, suggest that prior treatment with adjuvant cancer chemotherapeutic agents places the patient at-risk for posttreatment visual impairments. These studies, however, are not capable of assigning causality to the agents. Another way at getting at the question is to ascertain if the commonly used chemotherapeutic agents can cause ocular or other visual-related toxicities.

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Chemo Fog: Cancer Chemotherapy-Related Cognitive Impairment, edited by Robert B. Raffa and Ronald J. Tallarida

Table 1. Sample of visual system impairments or visual processing that have been reported in studies on chemo fog/chemo brain

Study	Description
Wieneke and Dienst[2]	A broad battery of neuropsychological tests was used to evaluate the cognitive functioning of 28 Stage I and II breast cancer patients, 28-54 years old (mean = 42 years; 82% Caucasian, 18% African-American, Asian, or Hispanic) who had received conventional (no high-dose) adjuvant chemotherapy 2-52 weeks prior to the study. The test battery[7,8] (age-, education level- and gender-adjusted) was designed to detect mild/subtle cognitive impairments. Treatment had been mainly with a cyclophosphamide/methotrexate/5-FU (CMF) regimen. Some patients also received cyclophosphamide/adriamycin/5-FU (CAF), CAF alone, or tamoxifen at the time of the study. The battery of tests included assessment of visuospatial functioning using three measures: Rey CFT—direct copy (*Z* score); Block design (WAIS-R) (*T* score) and Digit symbol (WAIS-R) (*T* score). The patients displayed significant impairment in visual memory.
van Dam et al[5]	The prevalence of cognitive deficits in Stage II and III breast cancer patients (N = 70, plus 34 controls) younger than 55 years old (mean = 45-49) who had been treated with adjuvant chemotherapy plus tamoxifen 1.5-2 years prior to the study was assessed as part of a standard battery of 13 tests. The patients had been treated with a fluorouracil/epidoxorubicin/cyclophosphamide (FEC) regimen plus tamoxifen or the same regimen plus high-dose cyclophosphamide, thiotepa and carboplatin. Several tests in the battery involved visual ability, including the Complex Figure test copy and recall, Trailmaking (A and B) and the D2 test. One of the largest deficits in the treatment group was in visual memory.
Schagen et al[4]	This study used neuropsychologic tests and interviews to evaluate cognitive function in breast cancer patients compared to controls (age-matched axillary lymph node negative breast carcinoma). About half of the patients had been treated with adjuvant CMF alone, the other half with CMF followed by a median of 2.4 years of tamoxifen prior to the study. The battery of tests included the Fepsy visual reaction and visual searching tests and the visual reproduction of the Wechsler memory scale (WMS). The patient group displayed significant deficit in performance in several of these measures.
Brezden et al[3]	The cognitive function of Stage I or II breast cancer patients, 24-70 years old, who were at the time receiving standard-dose adjuvant chemotherapy (either cyclophosphamide/epirubicin/5-FU or CMF) (N = 31), had completed adjuvant chemotherapy (N = 4) a median of two years earlier and healthy controls (N = 36) was assessed using the High Sensitivity Cognitive Screen and the profile of Mood States. Compared to controls, the chemotherapy-treated group exhibited significant impairment in the test measures.

Chemotherapeutic Agent Toxicity on the Visual System

Given that many of the cancer chemotherapeutic agents are cytotoxic, it is not surprising that they have known deleterious effects at various levels of the visual system and cause ocular complications/toxicities. The toxicity of chemotherapeutic agents on visual system components has been reviewed at least as early as 1983[9] and in at least three major systematic comprehensive reviews from 1989 to 2006.[10-12] A recent report on a large cohort of patients[13] found that ocular toxicity during cancer chemo/adjuvant therapy is a common side effect. A summary of previous reviews[10-12] of toxicities is presented in Table 2.[9,11,14-33]

Table 2. Visual system toxicity of agents used in cancer chemotherapy

Drug	Class	Mechanism	Visual System Toxicity
Cyclophosphamide	Nitrogen mustard derivative	Alkylating agent	Blurred vision, keratoconjunctivitis sicca (perhaps 50% of patients),[9] blepharoconjunctivitis, pinpoint pupils, others.[14-17]
Docetaxel	Taxane	Mitototic inhibitor	Canalicular and nasalacrimal duct obstruction, due possibly to stromal fibrosis,[18,19] are rare ocular side effects.
Doxorubicin	Anthracycline	Intercalates DNA	Excessive lacrimation and conjunctivitis in about 25% of patients[11,20] when given as single agent. Serious ocular toxicity noted when co-administered with desferrioxamine (with its own ocular toxicity)[21] to enhance antitumor activity.[22]
5-FU (5-fluorouracil)	Pyrimidine analog	Antimetabolite (inhibitor of thymi-dine synthetase)	Causes ocular toxicity (usually mild to moderate) in an estimated 25-38% of patients when given alone or in a combination regimen. Includes blurred vision, pain, photophobia, excessive lacrimation, irritation, conjunctivitis, circumorbital edema, ectropion, keratitis,[9,23] inhibition of mitosis of retinal pigment epithelial cells and fibrocytes[24] and others.[25-30]
Methotrexate	Folic acid antagonist	Antimetabolite (inhibitor of dihydrofolate reductase)	Ocular toxicity develops within 2-7 d after initiation of therapy in up to 25% of patients undergoing high-dose i.v. therapy. Includes periorbital edema, pain, blurred vision, photophobia, conjunctivitis, blepharitis and decreased reflex tear secretion,[11] (possibly resulting from an antimiotic effect in the rapidly dividing cells of the cornea and conjunctival epithelium).[17] Spinal administration can produce optic neuropathy and internuclear opthalmoplegia (that can be potentiated by concurrent cranial irradiation).[31,32] Multiple foci of axonal degeneration and demyelination in the optic nerve and chiasm[33] developed in a severe case of meningeal metastasis of breast carcinoma treated with an intraventricular combination with cytosine arabinoside.

Each review[10-12] suggests that combinations of cancer chemotherapeutic drugs might produce greater toxicity on the visual system than the individual drugs given alone. Based on synergistic interactions among the drugs on other endpoints,[34-39] it would reasonable to suspect that there might also be synergistic toxic effects—between drugs or between the visual and other brain systems. Such a possibility should be explored using animal models[40] and the data should be analyzed using rigorous joint action analysis and appropriate statistics.[41-47]

Conclusion

It is generally assumed that the chemo fog/chemo brain in patients who had received cancer chemotherapeutic agents as part of their treatment regimen is due to problems in handling information rather than input of information. Perhaps the agents (also) cause deficits in the input of information that impairs further CNS processing or interferes with the usual battery of neuropsychological tests. That is, some of the effects on cognitive domains might be secondary manifestations of, or exacerbations of, chemotherapeutic agent-induced toxic effects on the visual system. As briefly summarized in this chapter, there is ample evidence to consider this a possibility. Namely, many of the commonly used cancer chemotherapeutic agents produce toxicities on components of the visual system. Whether the agents produce these toxicities at clinical chemotherapeutic doses and whether any such toxicity is sufficient to produce one or more of the spectrum of effects in chemo fog/chemo brain is open to further study. Particular attention should be directed to the study of combination regimens. It seems quite plausible that combinations of these agents might produce synergistic visual toxicity just as they produce synergistic cytotoxic activity.

Acknowledgement

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Chapter 15

The Possible Role of Cytokines in Chemotherapy-Induced Cognitive Deficits

Jamie S. Myers*

Abstract

Proinflammatory cytokines play a significant role in the body's immune response to pathogens, including malignant cells. Proinflammatory cytokines are associated with tumor invasion and progressive disease and are released in response to many antineoplastic agents. Exogenous administration and endogenous production of cytokines is related to a pattern of behaviors known as sickness behavior that has a significant impact on patients' quality of life. The behavioral patterns associated with sickness behavior include inability to concentrate and impaired learning. Identification of sequelae specific to individual cytokine activity provides novel targets for investigation.

The Role of Proinflammatory Cytokines

The release of proinflammatory cytokines is one of several mechanisms hypothesized to play a role in the cognitive changes seen in patients receiving chemotherapy for treatment of malignancy. Proinflammatory cytokines are an integral component of the immune response and are released as a result of tissue injury related to tumor growth as well as the administration of antineoplastic agents.[1-5] The side effects that result have been referred to as sickness behavior, an adaptive response to disease and injury.[6,7] Further understanding of the sequela related to proinflammatory cytokine release will be important to the identification of patients at risk and the development of appropriate interventions.

Overview of Cytokines

Cytokines are small proteins involved in intracellular signaling. The term cytokine refers to both proinflammatory and anti-inflammatory signaling molecules that have autocrine, paracrine and endocrine activity. Cytokines are pleiotrophic, in that the same cytokine may be secreted by a number of different cell types and any one cytokine may act on multiple cell types. The primary function of cytokines is the mediation and regulation of immunity, inflammation and hematopoiesis.[8]

The Immune Response

The body's first line of defense against an invading pathogen (or antigen) is the macrophages which phagocytize the offending bacteria or virus (recognized as "not self" by the body's immune system).[9] This process is referred to as nonspecific immunity and ultimately results in the presentation of antigenic components to circulating T-cells. Antigen recognition results and additional specific T-cells are produced, leading to direct antigen cell death by cytotoxic T-cells.

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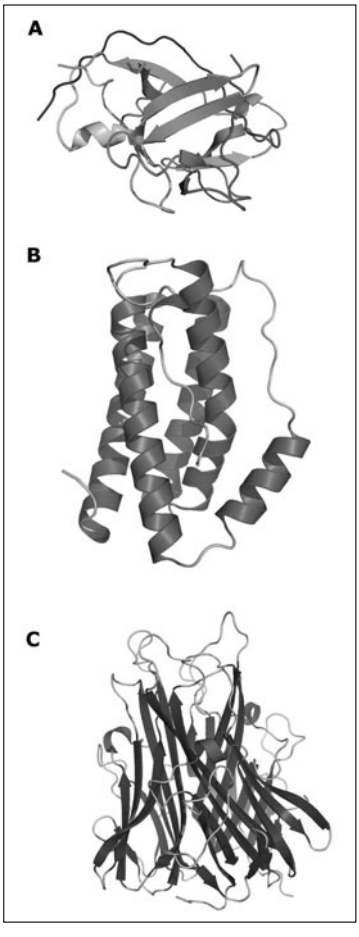

Figure 1. Crystal Structures of (A) Interleukin-1, (B) Interleukin-6 and (C) TNF-alpha. Reprinted with permission from Wikipedia. Retrieved on April 16, 2009 from http://en.wikipedia.org/wiki/File:2ILA.png.

Additionally, T-helper cells stimulate B-cell production associated with the secretion of antibody to destroy the antigen. Macrophages, T-helper cells and B-cells secrete a number of cytokines involved in the stimulation of cellular interactions needed for antibody production. The macrophages synthesize and release proinflammatory cytokines, including interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) (Fig. 1).[9] Proinflammatory cytokine release attracts additional immune cells to mount the immune response (referred to as specific immunity).

Proinflammatory Cytokines and Cancer

Release of proinflammatory cytokines is associated with the body's response to cancer and the tissue damage caused by malignancy.[2] Aberrant production of endogenous cytokines can serve as autocrine growth factors and are indicators of an immune response to tumor invasion.[10] Some tumor cells have been shown to secrete cytokines as invasion of surrounding tissues and metastasis occurs.[11,12] TNF-α is produced by tumor cells (such as ovarian and renal cancer). TNF-α is associated with poor prognosis, loss of hormone responsiveness, cachexia/asthenia and

can promote tumor spread. Interleukin 1 beta (IL-1β) promotes angiogenic factor production and is associated with increased tumor invasiveness and metastasis.[13] Chronic inflammation, seen in inflammatory diseases such as Helobacter pylori infection (gastric) and inflammatory bowel disease (colon) has been associated with progression to malignancy.[13] Elevations of IL-6 are seen in diffuse large B-cell lymphoma and pancreatic cancer.[10] Increased levels of cytokines as well as cognitive impairment have been seen in patients with leukemia and myelodysplastic syndrome prior to receiving antineoplastic therapy.[14]

Proinflammatory Cytokines and Antineoplastic Agents

Proinflammatory cytokine release in vitro has been associated with a number of antineoplastic agents.[3-5,15] Animal studies have shown production of cytokines following etoposide administration. Subsequent decreases in food intake and physical activity were observed.[7] Increased levels of IL-6, IL-8 and IL-10 have been associated with the taxanes (paclitaxel and docetaxel).[16] Chemotherapy-induced side effects are very similar to those associated with sickness behavior.[7]

Doxorubicin administration in animal models has been associated with an increase in circulating levels of TNF-α.[17] TNF-α has been shown to penetrate the blood brain barrier (BBB) and activate glial cells to produce TNF-α in the brain. Nitric oxide synthase is induced, nitric oxide is generated and central nervous system (CNS) injury results.[18] Oxidative stress is related to a number of additional antineoplastic agents in addition to the anthracyclines, such as cyclophosphamide, cisplatin, busulfan, mitomycin, fluorouracil, cytosine arabinoside and bleomycin.[17]

Proinflammatory Cytokines and Sickness Behavior

The behavioral patterns of animals and humans in response to the onset of infectious diseases has been referred to as sickness behavior.[6] The patterns included: lethargy, depression, anorexia, reduction in grooming, increased sleep, seeking warmth, conservation of energy, weakness, inability to concentrate, decreased interest in surroundings, decreased social and sexual interaction, decreased ability to experience pleasure, enhanced pain perception and impaired learning.[6,12,19-21] The febrile response is associated with many of these behaviors.[19]

Much of the knowledge about the role of cytokines in sickness behavior is credited to experience with the endogenous administration of cytokines as a component of cancer therapy. Treatment with immunomodulating agents such as interferon-α, TNF and IL-2 are associated with a side effect called "flu-like syndrome" that is similar to the behaviors associated with sickness behavior.[22] Fever, chills, lethargy, anorexia and cognitive impairment have been observed. Animal research has been conducted to evaluate the effects of endogenously administered IL-1β. The resultant hippocampal production of IL-1β was shown to interfere with memory formulation.[15]

The behavioral reaction to endogenous cytokines, such as fever, raised the question of how cytokine release in the peripheral blood would have an effect on the CNS.[23] The CNS is considered to be an immunoprivileged site due to the almost complete absence of T and B lymphocytes and the protection from foreign substances provided by the BBB. Cytokines are large molecules that should be unable to pass through the tight junctions of the BBB. Recent studies have demonstrated significant cross talk and bidirectional communication between the CNS and the immune system as well as the presence of cytokine receptors in the brain.[15,23-25] Proinflammatory cytokines (IL-1, IL-6, TNF-α) have been shown to penetrate the BBB in spite of their large molecular size. Additionally, some cytokines are produced in the CNS (TNF-α, IL-1β).

A number of mechanisms have been proposed for the BBB penetration. IL-1α is known to cross the BBB via a saturable transport system. Evidence also suggests this humoral route for IL-1β, IL-6 and TNF.[1,15] In some areas of the brain, the BBB is weak or absent such as the organum vasculosum lateralis terminalis, subfornical organ, median eminence, area postrema and choroid plexus.[15] Cytokines are able to cross the BBB at these circumventricular organs.

Neural routes are activated to project cytokine signaling to distant target regions within the brain through the use of mediators such as prostaglandin E2 and neurotransmitters.[1,9,15] The vagus nerve carries efferent signals from the periphery to the brain. Innervation of the lungs (a

typical site of pathogen entry) and the lymp nodes (tissue involved with the immune response) may explain why severing the vagus nerve eliminates many of the behavioral responses associated with exogenously administered cytokines.[1,26]

One of the cytokines produced in the brain is IL-1β. Production is thought to occur from microglial cells, perivascular and meningeal macrophages.[27] Once the cytokines are produced, they are postulated to travel to the periphery and initiate a neural cascade of brain-mediated host responses.[1]

Proinflammatory Cytokines and Other Symptoms

A number of additional symptoms have been associated with chemotherapy-induced proinflammatory cytokine release such as peripheral neuropathy.[12] Cisplatin and paclitaxel increase serum levels of IL-1β, interferon γ and TNF-α. Vincristine is associated with increased levels of TNF-α. Nuclear factor-κB is hypothesized to be the link between inflammatory cytokines and cancer-related symptoms due to its role in the stimulation of cytokine release for the immune and stress responses.[12] Cisplatin, paclitaxel and vincristine directly activate the nuclear factor-κB signaling pathway associated with neural tissue pain activation.[12]

Proinflammatory cytokine release has been linked to fatigue and cachexia.[12,28] Cachexia is associated with both IL-6 and TNF-α. Close linkages between depression and cachexia have been observed in patients with cancer.[28] Recent research has been devoted to clusters of symptoms that occur concurrently in patients with cancer.[29-31] Sickness behavior has been described as a symptom cluster[12,14] as have pain, fatigue and depression.[32]

Future Implications

A number of pharmaceutical agents are being evaluated for efficacy in minimizing the negative effects of proinflammatory cytokine release by targeting or antagonizing the action of cytokines. Many of these agents are being studied in chronic inflammatory diseases as well as malignancy.

Etanercept is a TNF receptor antagonist being studied in rheumatoid arthritis as well as cancer. This receptor-antibody fusion protein has been studied in combination with IL-2. Decreased levels of TNF-α and partial suppression of IL-1, IL-6, IL-8 and C-reactive protein were demonstrated. Etanercept also is being studied in cancer-related cahexia.[28] Infliximab is a TNF-α antibody approved for use in rheumatoid arthritis, Crohn's disease and ankylosing spondylitis. Some efficacy has been seen in the treatment of cachexia.[28]

Other anticytokine strategies under evaluation include: cytokine synthesis inhibitors, soluble cytokine receptors, cytokine receptor antibodies, cytokine receptor antagonists, IL-6 inhibitors and nuclear factor-κB inhibitors.[12,28]

Conclusion

Success in the area of cytokine inhibition has the potential for a major impact on quality of life in patients with malignancies. Much work remains to be done to determine the impact of specific cytokines, identify appropriate targets for therapy and demonstrate effectiveness of therapies to control or prevent the effects of cytokine-induced inflammatory response.

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Chapter 16

Pharmacokinetics of Anti-Cancer Drugs Used in Breast Cancer Chemotherapy

Swati Nagar*

Abstract

Pharmacokinetics of anticancer drugs used in breast cancer therapy are well established. This chapter reviews preclinical and clinical pharmacokinetics of the following drugs: cyclophosphamide, docetaxel, doxorubicin, 5-fluorouracil, methotrexate and tamoxifen. The absorption, distribution, metabolism and elimination of drugs are discussed in the context of breast cancer. The effect of age and menopause status on drug pharmacokinetics is evaluated. The important role of pharmacokinetic-pharmacodynamic modeling in understanding the phenomenon of chemo fog, memory deficit in breast cancer chemotherapy, is explored.

Introduction

Pharmacokinetics (PK), the study of the time course of drug absorption, distribution, metabolism and excretion, is a critical tool for optimization of drug therapy. Pharmacodynamics (PD) is the study of the pharmacologic effect (Fig. 1A). Pharmacokinetics and pharmacodynamic modeling are especially useful in clinical oncology, because anticancer drugs typically have narrow therapeutic windows. Further, drug exposure and clinical outcome are usually related. Thus, drug safety and efficacy need to be optimized to yield desired therapeutic outcome with the administered dosage, with minimal adverse effects. Pharmacokinetic-pharmacodynamic (PK-PD) evaluation of drugs allows this optimization (Fig. 1B).

The pharmacokinetics of anticancer drugs used in breast cancer therapy are well defined. The utility of PK studies in designing preclinical studies, human dosage regimen design and dose adjustment in special populations is explored with specific examples in this chapter. Future directions such as PK-PD evaluation of breast cancer drugs and the phenomenon of chemo fog are additionally discussed.

Pharmacokinetics of Anticancer Drugs Used in Breast Cancer Chemotherapy

Of the numerous anticancer drugs currently in clinical use, PK of drugs commonly used in breast cancer therapy (Fig. 2) are discussed below.

Cyclophosphamide

Cyclophosphamide is a prodrug that is activated via cytochrome P450 (CYP) enzymes to its active forms.[1,2] It is extensively metabolized to both active as well as inactive metabolites. Its elimination half life is 5-9 h and is shorter in children compared with adults.[3] The prodrug is not highly protein bound and renal excretion is low, possibly due to extensive reabsorption. With advances

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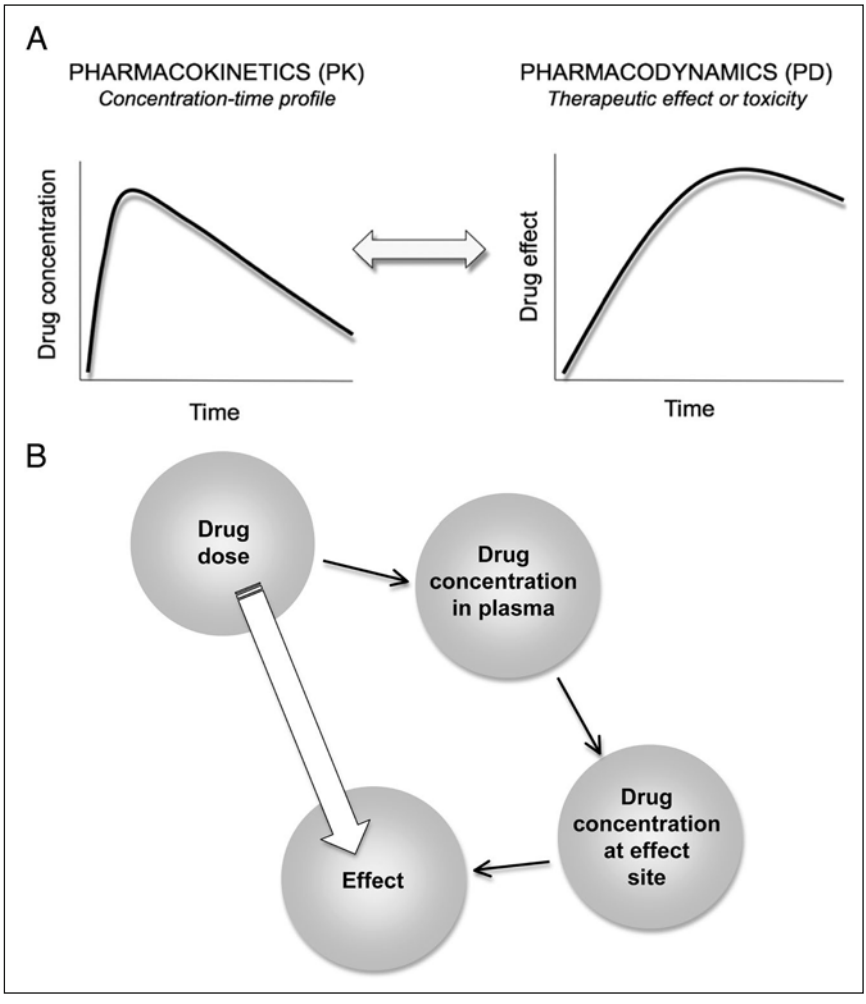

Figure 1. Pharmacokinetics studies the time-course of chemotherapeutic drug plasma concentration after a dose has been administered. Pharmacodynamics is the evaluation of the pharmacologic effect (therapeutic or toxic) that the drug elicits with respect to time (A). A PK-PD model uses a 'link' effect site compartment to relate the drug's concentration to its effect (B).

in bioanalytical methods, studies have recently focused on the PK of active metabolites instead of the inactive prodrug.[3] Large inter-individual variability has been noted in cyclophosphamide PK and CYP pharmacogenetics explains at least part of this variability.[1] Cyclophosphamide is known to cause autoinduction and is susceptible to drug-drug interactions because it is metabolized via CYPs.

Cyclophosphamide PK has been evaluated extensively in preclinical models. The role of CYP enzymes in the PK of cyclophosphamide was characterized in an elegant study utilizing cytochrome P450 reductase null mice.[4] In male wild-type mice, intraperitoneal doses of 100 and 300 mg/kg yielded areas under the plasma-time curve (AUCs) of 1560 and 8100 μg · min/ml respectively. The maximum plasma concentration (Cmax) was 38 and 181 μg/ml respectively at these doses. The intrinsic clearance of the drug was 6-fold greater in wild-type mice compared with the cyp-activity

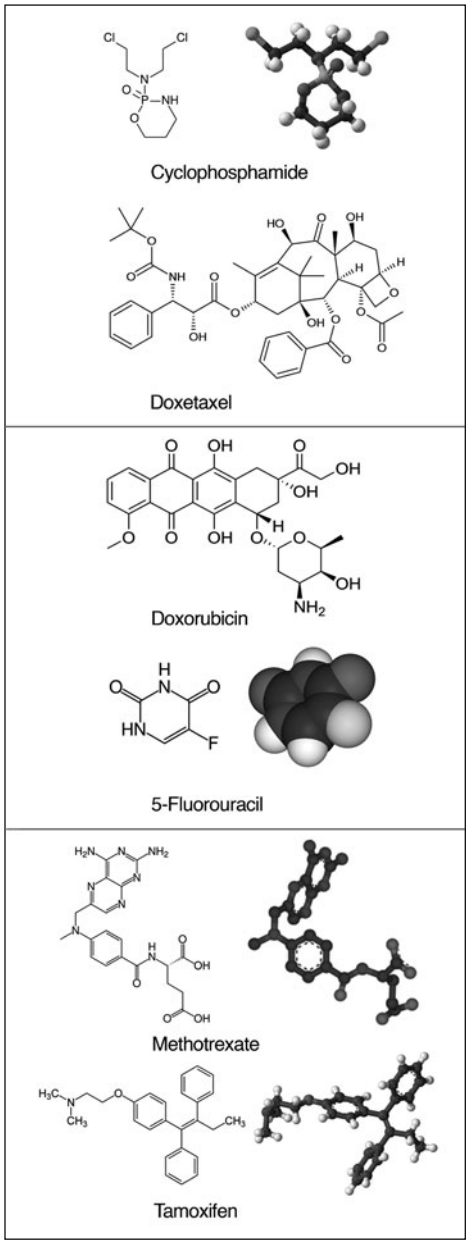

Figure 2. Chemical structures of cyclophosphamide (N,N-Bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide), docetaxel ((2R,3S)-N-Carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5, 20-epoxy-1, 2, 4, 7, 10, 13-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate), doxorubicin ((8S,10S)-10-(4-Amino-5-hydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione), 5-fluorouracil (5-Fluoro-1H-pyrimidine-2,4-dione), methotrexate ((2S)-2-[(4-{[(2,4-Diamino-7,8-dihydropteridin-6-yl)methyl](methyl)amino}phenyl)formamido]pentanedioic acid), and tamoxifen ((Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethyl-ethanamine).

null mice. Profound differences in the PK of cyclophosphamide between the two groups led to direct evidence of the critical role of CYP enzymes in cyclophosphamide disposition. A recent study developed a different genetically modified mouse model, again with no cyp activity.[5] The PK of cyclophosphamide was similar to previous reports in the wild-type mice. This study corroborated previous reports of the importance of CYP enzymes in cyclophosphamide PK.

Clinically, cyclophosphamide is administered orally or intravenously, most often in combination with doxorubicin, 5-fluorouracil, or adriamycin. Doses ranging from 100-600 mg/m^2 are administered to breast cancer patients[6] and its PK in humans is well established.[3] A study with 1 g/m^2 cyclophosphamide IV 1-h infusion in 29 Caucasian hematological cancer patients reported an AUC of 367 μg · h/ml and Cmax of 37 μg/ml. Drug clearance was estimated to be 6 L/h.[7] Another study was conducted in 51 Japanese breast cancer patients[8] and levels of cyclophosphamide as well as its 4-hydroxy metabolite were measured. The dose range was 600-1500 mg (300-750 mg/m^2), delivered as a one-hour IV infusion. Mean cyclophosphamide AUC was 775 μmol · h/L and a mean clearance of 4 L/h. The mean AUC for the 4-hydroxy metabolite was 9.4 μmol · h/L.[8]

Docetaxel

Docetaxel is a semi-synthetic analog of paclitaxel and is a cytotoxic antimicrotubule agent.[9] It exhibits complex PK in humans. Docetaxel is highly protein bound and α1-acid glycoprotein levels are found to predict docetaxel total clearance.[10] The drug is mainly metabolized by CYP3A4 and 3A5 and metabolites are eliminated fecally. Urinary elimination of the parent and metabolites is <10%.[11] CYP pharmacogenetics and docetaxel PK have been evaluated extensively, but the role of CYP polymorphisms in variable docetaxel disposition remains to be clearly defined.[10] Docetaxel is also a substrate for the efflux transporter P-glycoprotein.

Docetaxel PK has been evaluated in preclinical models, especially to delineate the role of efflux transporters and metabolizing enzymes in its disposition.[12] Docetaxel exhibits linear PK in mice.[13] It is highly protein bound and distributes well into most tissues. Like humans, docetaxel is metabolized and undergoes predominantly hepatobiliary elimination. Docetaxel (10 mg/kg) was dosed orally and IV in control and Pgp knockout mice in a recent study.[14] Oral docetaxel was well absorbed in control mice despite the presence of Pgp. It undergoes extensive first-pass metabolism resulting in poor oral bioavailability. Inhibition of its metabolism is a useful strategy to increase its AUC and exposure.

Clinically, docetaxel exhibited a total clearance of about 29 L/h/m^2 upon a 35 mg/m^2 weekly or 3-weekly schedule.[10] The elimination half-life was 15.6 h based on a 24 h sampling schedule. A mean AUC of 1.32 μg · h/ml was obtained, with a Cmax of 1.85 μg/ml. Studies in elderly patients did not show an effect of age on drug clearance.[15] Docetaxel dose adjustment is required in patients with liver function impairment.[10]

Doxorubicin

Doxorubicin is an anthracycline antibiotic that intercalates with DNA and inhibits topoisomerase II. It is delivered either as the free salt form or as a liposomal formulation.[16] Clearance as well as apparent volume of distribution is lower for liposomal doxorubicin compared with the free form. Doxorubicin is metabolized to cytotoxic doxorubicinol and inactive aglycones.[17] It is known to induce several CYP superfamily members.[18] It is a substrate for the efflux transporter P-gp.

In preclinical studies doxorubicin (0.9 mg/kg dose in rats) was shown to exhibit biphasic PK profiles, with a distribution half life of 5-10 min and an elimination half-life of 29 h.[16] The clearance was about 120 ml/h/kg and the volume of distribution was 5 L/kg. A study in tumor-bearing mice utilized an IV dose of 6 mg/kg doxorubicin formulated in liposomes and yielded an AUC of 3.02 mg · h/ml.[19] The same dose given as free doxorubicin yielded a lower AUC (1.4 mg · h/ml) in tumor-bearing mice in an independent study.[20]

Clinical PK of doxorubicin is well established. Pegylated liposomal doxorubicin was administered as an IV infusion every 4 weeks to 15 patients with advanced solid tumors.[21] The PK profile was monophasic, with a long elimination half-life, low clearance and small volume of distribution. For a dose range of 30-50 mg/m^2, observed plasma AUC was 2513-4663 μg · h/ml, with Cmax in

the range of 19-35 μg/ml and systemic clearance estimate of 13 ml/h/m^2. Similar PK parameters were estimated in an independent study involving liver cirrhosis patients.[22]

5-Fluorouracil

5-fluorouracil (5-FU) is a pyrimidine analog that inhibits DNA synthesis. 5-FU must be converted to its active nucleotide for cytotoxic activity. It is administered IV and a continuous infusion achieves plasma concentrations of 0.5-0.8 μM.[23] 5-FU readily enters the cerebrospinal fluid. Urinary excretion of a single dose is low, about 5-10%. It is inactivated mainly in the liver via dihydropyrimidine dehydrogenase.

In tumor-bearing mice, an oral 13 mg/kg dose of 5-FU was reported to yield a plasma AUC of 55 ng · h/g.[24] In another study, free 5-FU administered IV (40 mg/kg) to control mice displayed one-comparment PK, with an AUC of 639 mg · min/L and an initial plasma concentration of 36 mg/L.[25] A dose of 100 mg/kg of 5-FU administered intraperitoneally to tumor-bearing mice yielded an AUC of 2922 mg/min/L and a Cmax of 124 μg/ml.

Clinical PK of 5-FU has been established in cancer patients. A study in 22 patients with upper gastrointestinal tract adenocarcinomas was conducted in order to establish an association between 5-FU toxicity and its plasma AUC.[26] A dose range of 315-560 mg/m^2 was administered as a 1-h infusion. Plasma AUC in the range of 147-405 mg · min/L was observed, with Cmax ranging from 2.8 to 6.8 μg/ml. The study concluded that increasing the infusion period for 5-FU administration decreased the AUC and therefore its toxicity. A subsequent larger study by another group enrolled 181 colorectal cancer patients.[27] The initial 5-FU dose was selected to attain a target AUC of 596 mg · min/L. However, this study concluded that 5-FU toxicity was not completely associated with its PK and other clinical correlates were necessary to understand its toxic profile.

Methotrexate

Methotrexate is an antifolate drug used in several cancers besides breast cancer.[23] After IV administration it displays triphasic plasma-time curves. About 50% of the drug is plasma albumin-bound. Metabolism is minimal and 90% of the drug is excreted unchanged in the urine. Methotrexate concentrations in the cerebrospinal fluid are low, but cytotoxic levels can be achieved in the CNS with high doses followed by leucovorin rescue.

Methotrexate PK has been reported in preclinical models and appears to be highly variable. For example, a 100 mg/kg intraperitoneal dose in mice yielded plasma AUC in the range of 156-207 μg · h/ml in one study.[28] Another study at a dose of 400 mg/kg i.p. however resulted in a plasma AUC of 238 μg · h/ml.[29] A recent study evaluated i.p. doses in the range 10-600 mg/kg in mice and reported AUCs at 267-12500 μg · h/ml.[30]

Methotrexate disposition was evaluated in 44 pediatric patients with acute lymphoblastic leukemia (ALL).[31] A high dose of 5 g/m^2 resulted in high plasma exposure of drug. The authors evaluated genetic polymorphisms in the human transporter multidrug resistance related protein 2 (MRP2; ABCC2) gene and found a significant gender—specific effect of the -24C > T polymorphism on methotrexate PK. Female patients with at least one copy of the -24T allele had significantly higher AUCs (measured between 36-48 h after start of infusion) than other patients.[31] Methotrexate population PK was evaluated in another study enrolling 79 pediatric ALL patients.[32] A 2-compartment model described drug PK, with a clearance estimate of 8.8 L/h and initial volume of distribution 17.3 L. A 24-h infusion of a 5 g/m^2 dose resulted in an AUC of 588 μg · h/ml. The population PK model made it possible to predict that below a threshold methotrexate level of 0.2 μM, folinic acid administration (delivered to minimize methotrexate-related toxicity) can be stopped.[32]

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator and is commonly used in hormone-responsive breast cancer therapy. The usual dose is 10 mg twice a day, but doses as high as 200 mg per day have been prescribed. It is readily absorbed upon oral administration, with steady-state levels reached at 4-6 weeks.[23] Tamoxifen is metabolized to oxidative metabolites (some of which

are active) via CYP enzymes, which undergo further Phase II glucuronidation and sulfation. The drug and its metabolites undergo enterohepatic recirculation and elimination is predominantly in the feces.

Early preclinical studies reported a lack of detectable tamoxifen concentration at low doses. Slow-release pellets containing 5 or 25 mg tamoxifen were administered subcutaneously to mice, but no plasma drug levels were detectable even after 2 weeks of treatment.[33] Daily s.c. injections of 1000 μg or i.p. 25-100 mg/kg doses resulted in plasma concentrations of 0.21-0.51 μM. In another study, single high dose of tamoxifen in mice (200 mg/kg oral) resulted in detectable levels of parent drug as well as metabolites 4-hydroxytamoxifen and *N*-desmethyltamoxifen.[34] Parent drug plasma AUC was 15.9 μg · h/ml in mice. Metabolite formation in rats was found to be more representative of human metabolism, suggesting that rats rather than mice might be a better preclinical model for tamoxifen disposition studies.

Tamoxifen PK has been well documented in humans.[35-40] In a clinical trial including 34 postmenopausal metastatic breast cancer women, 20 mg tamoxifen was administered daily for 6 weeks.[38] Median concentrations of 107 ng/ml parent, 200 ng/ml *N*-desmethyltamoxifen and 3 ng/ml for 4-hydroxy tamoxifen were observed. High-dose tamoxifen PK was evaluated in 34 male patients with hormone-refractory metastatic prostate cancer.[36] Tamoxifen at 16 mg/m^2/day was administered and yielded an average steady-state concentration of 2.96 μM. Results from a large clinical trial involving 24 international centers and a total of 357 patients were recently published.[35] Tamoxifen alone (20 mg/day) was administered to 111 postmenopausal women with early stage breast cancer. The geometric mean steady-state trough plasma concentration of tamoxifen was 95 ng/ml, while that of *N*-desmethyltamoxifen was 265 ng/ml. A dose range study (1-20 mg/day tamoxifen) was conducted recently in pre as well as postmenopausal women (total n = 120).[39] Median tamoxifen concentration ranged from 7.5 to 83.6 ng/ml in serum and 78.2-744.4 ng/ml in breast tissue. This study further quantitated levels of the 4-hydroxy, *N*-desmethyl and *N*-didesmethyl metabolies in serum, normal breast tissue and breast cancer tissue. Finally, 32 postmenopausal breast cancer patients on 20 mg/day tamoxifen were enrolled in a PK study and a steady-state plasma drug AUC of 3.04 mg · h/L was reported.[37]

Pharmacokinetics in Special Populations: Age and Menopause Status

Age related physiologic changes can alter the PK-PD of a drug. Age therefore becomes an important consideration before starting systemic chemotherapy in breast cancer patients.[41] Drug absorption is affected with age due to decreased gastrointestinal motility, decreased digestive enzyme secretion and decreased blood flow.[42,43] Changes in body composition, decrease in total body water and lower body mass all contribute to altered drug distribution. Hepatic metabolism may be affected with age due to a decrease in liver mass, hepatic blood flow and enzyme function.[41] Tumor biology additionally changes with age.[44] These age-related changes in drug PK-PD also play a critical role in drug-drug interactions, especially in the older patient who is more likely to be on numerous drugs at a given time. Pharmacokinetic data have been collected in elderly breast cancer patients. In some cases, decreased drug clearance has been noted, while other studies have not found a significant effect of age on drug PK.[41,44] It is nevertheless critical to take into account patient age when making decisions regarding chemotherapy drug selection, dosing, single versus combination therapy and therapeutic monitoring for toxicity or adverse events.

Choice of therapy (chemotherapy, hormone therapy, monoclonal antibody) for breast cancer depends on the cancer status, i.e., stage (early versus metastatic), estrogen/progesterone receptor status (positive versus negative) and human epidermal growth factor receptor 2 (Her2/neu) status (positive versus negative). Menopause status—whether a woman is premenopausal, perimenopausal, or postmenopausal—also dictates choice of breast cancer therapy. For example, aromatase inhibitors improve the outcome for early-stage breast cancer in postmenopausal women, but should not be given to premenopausal women as they may stimulate tumor growth.[45,46] Relative amounts of estrogen hormones depend on menopausal status and it remains to be studied whether differential levels of estrogens would alter the PK of an administered drug. Tamoxifen has been shown

to increase estrogen hormone clearance.[47] Estrogens are glucuronidated and sulfated in humans and might interact via these common metabolic pathways with drugs that are also substrates for glucuronidation and sulfation (e.g., tamoxifen). The picture is further complicated by genetic polymorphisms in sulfating and glucuronidating enzymes and their effects on hormone and drug metabolism.[48-52]

Pharmacokinetics of Anticancer Drugs and Memory Deficit as a Pharmacodynamic Endpoint

There is renewed interest in the evaluation of memory deficit as a result of breast cancer chemotherapy. Several reports have recently evaluated cognition in relation to chemotherapy.[53-56] There is debate as to whether any cognitive deficit is associated with chemotherapy, or is instead correlated with stress, hormone changes and age in the older patient. Further, mechanisms underlying cognitive deficits are not yet understood. To date, there have been no studies correlating pharmacokinetics of anticancer drugs with cognition as a pharmacodynamic endpoint. Such studies will be critical to discern the role of PK in any memory deficits due to chemotherapy. It is conceivable that differential effect site drug (or active metabolite) concentrations will correlate with altered cognitive endpoints. Furthermore, study design of such PK-PD studies must incorporate effect site (e.g., brain) drug concentrations instead of only evaluating plasma drug levels.

Conclusion

Pharmacokinetics of drugs used in breast cancer therapy have been evaluated in detail. Memory deficit due to breast cancer chemotherapy is a new area of research. PK-PD studies correlating memory deficit to effect-site anticancer drug concentrations have not been conducted to date. Such studies will be critical in understanding the phenomenon of chemo fog, its underlying mechanisms and in designing therapeutic regimens to minimize these adverse effects.

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Chapter 17

Combination Analysis

Ronald J. Tallarida*

Abstract

This chapter describes quantitative methodology that is directed toward assessing interactions between a combination of agonist drugs that individually produce overtly similar effects. Drugs administered in combination may show exaggerated, reduced or predictable effects that are dependent on the specific drug pair and the doses of the constituents. The basis for quantitating these unusual interactions is the concept of dose equivalence which, in turn, is determined from the individual drug dose-effect relations. A common analytical procedure that follows from dose equivalence uses a graph termed an *isobologram*. We present here an overview of the isobologram, its use and certain related methods that apply to classifying various drug interactions.

Introduction

Many therapeutic situations use two or more drugs in combination. The main reason for using combinations is that each agent contributes to the effect and, in general, the administration of a combination allows the use of lower doses. This may be especially important in reducing toxicity. In selecting cancer treatment combinations there are several drug mechanisms that help reduce the cancer, e.g., damaging the DNA of the affected cancer cells, inhibition of the synthesis of new DNA strands to stop the cell from replicating and stopping mitosis, which is the actual splitting of the cancer cell. When quantitating the effect of a drug or combination some specific and common endpoint (effect) is used to assess the efficacy of the treatment as a function of dose or dose combination. In testing a drug combination the combination effect is often described as *additive* although in some situations the combined effect might be *synergistic* or *sub-additive*. In this section we describe these terms and the kind of analysis that leads to these designations. We will designate the drugs as "drug A" and "drug B" and, in referring to doses of these, we use the same (upper or lower case) letters in italics; thus a and A are doses of drug A, while b and B are doses of drug B.

Drug Additivity

The theoretical basis for predicting the effect of a combination is rooted in the concept of *dose equivalence*. By that is meant the determination of the doses of each drug alone that give the same effect. Thus, it is necessary to have the dose-effect relation of the individual drugs. In some cases the ratio of equally effective doses is the same at every effect level. This is the simplest case to analyze and thus we discuss it first. This constant ratio applies if the dose response curves display linear segments as in Figure 1A or, more commonly, as in Figure 1B. In each of these situations the specified effect is achieved by doses denoted by A and B as shown. The ratio $A/B = R$ is the same at every effect level. Because this constant relation is assumed, every dose a of drug A has an equivalent in terms of drug B and this equivalent is clearly a/R. We denote this equivalent by $b_{eq}(a)$. It follows that a selected effect, such as E^* in the Figure, which required dose B alone (or dose A

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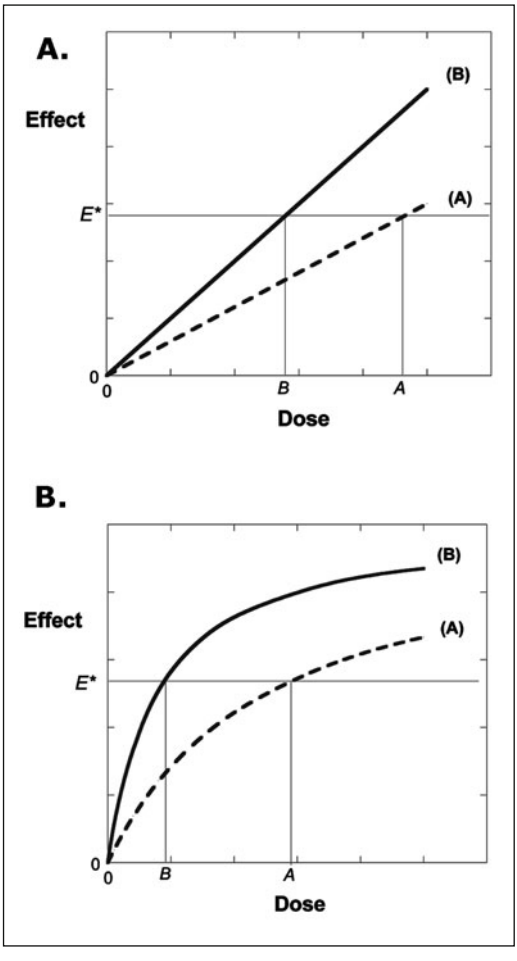

Figure 1. Dose-effect curves that show a constant potency ratio are described by the linear curves (A) and, more commonly, by hyperbolic curves (B) that attain the same maximum E_{max}. The curves are given by equations in terms of their respective doses, *a* and *b*; $E = \frac{E_{max} a}{a + C_A}$ for drug A and $E = \frac{E_{max} b}{b + C_B}$ for drug B. In these E_{max} is the maximum effect and C_A and C_B are constants that define the drugs' potency. In each case there is shown equally effective doses, *A* and *B,* for some specified effect *E** and these doses are used in constructing the isobole of Figure 2.

alone), can be achieved by doses *a* and *b* together provided that $b + b_{eq}(a) = B$; thus, $b + a/R = B$, which can be rearranged to

$$\frac{a}{A} + \frac{b}{B} = 1 \qquad (1)$$

The form given by equation (1) is graphically illustrated by the line shown in Figure 2. This line, termed an isobole, consists of dose pairs (a,b) that give the specified effect. Dose combinations along this line are called additive because we *add* the dose of one and its equivalent of the other. Additivity implies that there is no interaction between the drugs, i.e., each contributes to the effect according to its own potency. The isobole, introduced by Loewe,[2-4] has been widely employed in

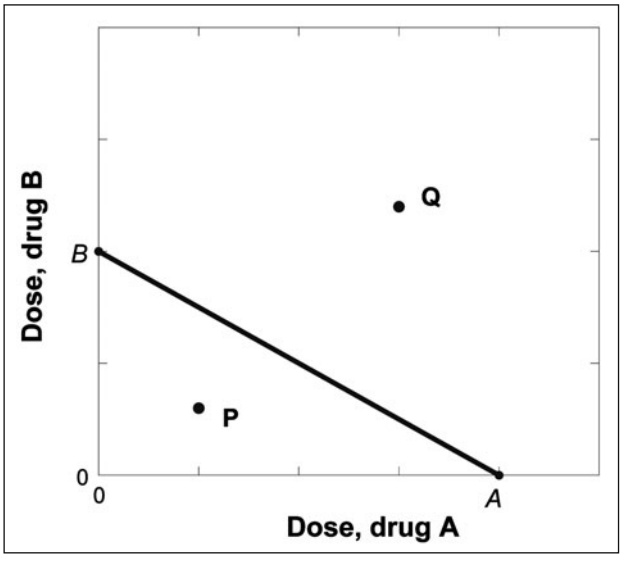

Figure 2. The isobole of additivity is shown as the line segment with intercepts *A* and *B* that represent the doses of drugs A and B, respectively, that achieve the specified effect when each drug acts alone. An experimental point (P) below the isobole indicates synergism while point (Q), above the isobole, indicates sub-additivity.

pharmacological testing of drug combinations and is especially widespread in preclinical tests such as those discussed in Chapter 18 by Walker.

Tests of Drug Combinations and the Isobole

The construction of the isobole is a useful procedure for evaluating the action of an actual combination. When the combination is tested the same effect used in determining the isobole is used to assess the effect of the combination. If the combination experiment reveals that the specified effect level is achieved with a dose pair designated (*a,b*) this experimental point (dose combination) is plotted on the coordinate system containing the isobole. If this experimental point lies on the isobole (or not significantly off it) then the combination produced the expected additive effect. However, the experimental point might be off the line. If it is above the isobole, which means that higher doses were needed, then we say that the interaction is *sub-additive*. In contrast we may find that the experimental point lies below the isobole, thereby showing that the effect is attained with lower doses than those predicted by simple additivity. This indicates *synergism.* Figure 2 illustrates each of these non-additive interactions. If the effect is a desirable effect (e.g., shrinking the tumor, enhancing cognition, etc.) then the finding of synergism is especially important and desirable because the therapeutic objective was achieved with doses that are less than expected, a situation that usually means lower toxicity. If the effect on which the isobolographic analysis was based used a toxic endpoint, then synergism is understandably undesirable. Whether the effect studied is therapeutic or toxic, a combination that is non-additive at one dose pair may be simply additive at another. In other words, the finding of synergism or sub-additivity is not merely an attribute of the two drugs; it also depends on the constituent doses. Because of this fact much preclinical testing of drug combinations has employed combinations in various ratios in order to find the optimal combination for synergizing a desirable effect.

Error Estimates

The isobole, as described above, is a convenient graph for assessing the nature of the interaction between the two drugs since it identifies the dose pair that is either on or off the isobole. However, the terms "on" and "off" need further analysis since all plotted points (dose pairs) have a variance. The experimental point will usually be determined from a regression analysis and therefore its variance is determined by standard regression methods (see, for example, ref. 5). The isobole of additivity, however, is derived from the parent dose-effect curves of the constituents and these, too, have error. Thus it is necessary to calculate the variance surrounding the additive isobole. A simple approximate method is given here and is based on the isobole intercept values A and B and their variances. These allow the selection of the dose pair. Dose a is selected to be some fraction f of A while dose b is taken to be $(1 - f)$ of B. It is easily seen from equation (1) that a dose pair selected this way is on the isobole and that the total additive dose, denoted Z_t, is given by

$$Z_t = fA + (1 - f)B \tag{2}$$

From equation (2) the variance follows as

$$V(Z_t) = f^2 V(A) + (1 - f)^2 V(B) \tag{3}$$

It is worthy of note that A and B are not precisely known and, thus, the selection of fA and $(1 - f)B$ and their use in equation (3), is approximate (but generally quite acceptable). It is further noted that this combination selection means that the proportion of the total that is drug A is $p_A = fA/Z_t$ and the proportion that is drug B is $p_B = (1 - f)B/Z_t$.

Dose-Effect Relation of the Drug Combination

Our previous discussion dealt with the isobolographic method. It is also possible to view the expected (additive) dose-effect relation of the drug combination. It should be noted that the effect of a combination is not obtained by adding the individual effects of doses a and b. This is evident, for example, when dose a alone yields an effect such as 60% of the maximum and dose b alone gives, say 70%, of the maximum. Summing these effects is without meaning. Instead we use the same concept of dose equivalence that was described previously. For example, if the individual dose-effect relations are hyperbolic as described in Figure 1B (the most common model) then the equation of either drug A or drug B can be used with the total dose expressed as $b + b_{eq}(a)$ in drug B's equation or $a + a_{eq}(b)$ in drug A's equation. From drug B's equation this would give the additive effect as

$$E_{add} = \frac{E_{max}\,(b + b_{eq}\,(a))}{(b + b_{eq}\,(a)) + C_A} \tag{4}$$

and thereby allow a direct comparison of this expected effect with the actual effect. The same result occurs if $a + a_{eq}(b)$ is used as the total dose in drug A's equation. For further details on this approach and the isobolographic approach the reader is directed to this author's monograph[5] and more recent review articles.[6,7]

Variable Potency Ratio

Thus far we have discussed situations in which the potencies of the individual drugs have a constant ratio. For many drug pairs this ratio varies over the effect range. An obvious example of this variation applies when the individual dose-effect curves are hyperbolic but have different maximum effects. In such situations one can find equally effective doses in the range of effects that are achieved by each drug and, thus, dose equivalence is used as previously described. However, the isobole of additivity is not linear in this case[1] but appears as shown in Figure 3.

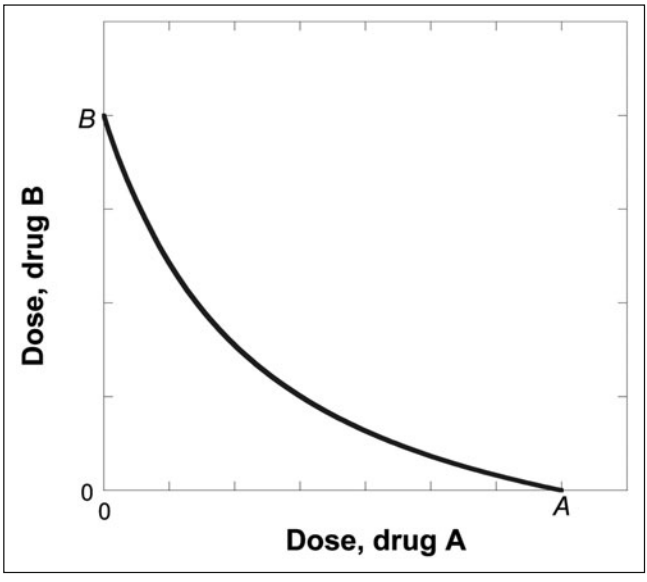

Figure 3. The isobole of additivity is curvilinear in situations in which the relative potency of the constituent drugs is variable. The isobole illustrated applies to an effect level that is achieved by dose *A* of drug A and dose *B* of drug B. If the selected effect is greater than the maximum achieved by drug A then the isobole has no intercept on the horizontal axis. Further detail on this case is contained in reference 1.

This isobole is used in the same way previously described in assessing whether an actual combination departs from additivity.

Conclusion

The detection of a synergistic or sub-additive combination of two agonists that individually yield overtly similar effects is often accomplished with isobolographic analysis. That procedure begins with determinations of the individual drug dose-effect relations from which the additive isobole for a specified effect is constructed. The isobole is then viewed against the experimental combination dose pair that gives the effect in determining departures from simple additivity. Synergism is especially important because such combinations yield the specified effect with lesser doses of the constituents, a result that may reduce toxicity.

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Chapter 18

Animal Models

Ellen A. Walker*

Abstract

As clinical studies reveal that chemotherapeutic agents may impair several different cognitive domains in humans, the development of preclinical animal models is critical to assess the degree of chemotherapy-induced learning and memory deficits and to understand the underlying neural mechanisms. In this chapter, the effects of various cancer chemotherapeutic agents in rodents on sensory processing, conditioned taste aversion, conditioned emotional response, passive avoidance, spatial learning, cued memory, discrimination learning, delayed-matching-to-sample, novel-object recognition, electrophysiological recordings and autoshaping is reviewed. It appears at first glance that the effects of the cancer chemotherapy agents in these many different models are inconsistent. However, a literature is emerging that reveals subtle or unique changes in sensory processing, acquisition, consolidation and retrieval that are dose- and time-dependent. As more studies examine cancer chemotherapeutic agents alone and in combination during repeated treatment regimens, the animal models will become more predictive tools for the assessment of these impairments and the underlying neural mechanisms. The eventual goal is to collect enough data to enable physicians to make informed choices about therapeutic regimens for their patients and discover new avenues of alternative or complementary therapies that reduce or eliminate chemotherapy-induced cognitive deficits.

Introduction

As survival rates from cancer increase due to the advances in detection and treatment, understanding and managing treatment related problems is a concern, especially in relation to cognitive dysfunction both during and after chemotherapy.[1] As clinical studies are finding evidence suggesting that cognitive deficits occur in patients, few preclinical models are available to objectively assess and study chemotherapy-induced learning and memory deficits. More recently, however, rodents are used to assess the role of a range of cancer chemotherapeutic agents in the disruption of various learning and memory processes (Table 1). Since the chemotherapeutic agents may impair several different cognitive domains in humans,[2,3] it is important to select preclinical models that are objective and includes several aspects of the learning and memory processes.

Normal learning and memory requires an intact nervous system and a coordinated progression through various phases such as acquisition, consolidation, retention and retrieval (for review see ref. 4). Since potential cognitive deficits from cancer chemotherapeutic agents can result from disruption at any one of these phases, it is important to examine an agent in either several different assays or a single assay that can incorporate several aspects of learning and memory. Furthermore, learning and memory models should allow for drug-administration at critical stages of the learning process and for repeated exposures to model most cancer chemotherapy regimens. In the studies described below, the effects of various chemotherapeutic agents in rodents on sensory processing,

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Table 1. Mechanisms of chemotherapeutic agents used in various rodent preclinical models

Agent	Class	Mechanism and Common Combinations
5-Fluorouracil	Antimetabolite	Pyrimidine antagonist. Covalently binds the enzyme thymidylate synthase. Metabolite is incorporated into RNA to interfere with translation.
Carboplatin and Cisplatin	Platinum analogs	Covalently binds to guanine, adenine and cytosine bases forming both intrastrand and interstrand DNA cross-links and inhibition DNA synthesis and function. Platinum complexes synergize with other anticancer drugs.
Carmustine	Alkylating agent	Cross links with functional reactive groups breaking DNA strands resulting in inhibition of DNA synthesis and function.
Cyclophosphamide	Nitrogen mustard alkylating agent	Alkylates guanine and other bases; cross-linking with two functional reactive groups, breaking DNA strands. Possesses potent immunosuppressive activity.
Cytarabine	Antimetabolite	Incorporates into RNA and DNA inhibiting DNA chain elongation and blockade of DNA synthesis and repair.
Docetaxal	Taxane	Mitotic spindle poison. Stabilizes microtubules preventing mitosis.
Methotrexate	Antimetabolite	Folic acid antagonist; blocks synthesis of thymidylate, purine nucleotides, serine and methionine.
Paclitaxel	Taxane	Mitotic spindle poison through high affinity binding to microtubules preventing mitosis and cell division.
Tamoxifen and Toremifene	Antiestrogens	Blocks estrogen receptors on estrogen-sensitive tumors producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects. Follows therapy with doxorubicin, cyclophosphamide, 5-fluorouracil and docetaxel.
ThioTEPA	Alkylating agent	Cross links with functional reactive groups breaking DNA strands resulting in inhibition of DNA synthesis and function.
Vincristine	Vinca alkaloid	Inhibition of tubulin polymerization disrupting microtubule assembly and mitosis.

conditioned taste aversion, conditioned emotional response, passive avoidance, spatial learning, cued memory, discrimination learning, delayed-matching-to-sample, novel-object recognition, electrophysiological recordings and autoshaping are described. Although the basic strategy of most of these studies is to examine the effects of one or two chemotherapeutic agents in one learning or memory model, a few studies examined multiple learning models or phases of learning.[5-7] It appears at first glance that the effects of the cancer chemotherapy agents in these many different models are inconsistent. However, a literature is emerging that reveals subtle or unique changes in various learning or emotional processing in preclinical models which are dose- and time-dependent.

Effects of Cancer Chemotherapeutic Agents on the Disruption of Sensory Processing in Animal Models

Certain cancer chemotherapeutic agents can impact sensory processing and this effect may alter cognitive processing. Peripheral neuropathies are the predominant neurotoxicity in humans and this neuropathy is more pronounced with higher cumulative doses of such agents as paclitaxel and docetaxel.[8,9] Docetaxel and paxclitaxel can be associated with nerve conduction abnormalities including reduced sensory and motor nerve action potentials and decreased motor nerve conduction velocity resulting in mild to moderate paresthesias, loss of tendon reflexes and loss of vibration sensation. In rodent preclinical models, treatment of paclitaxel and vincristine can produce neuropathies as measured by mechanical sensitivity[10,11] and this model can be used to screen analgesic agents.[12] Despite producing peripheral neuropathies, paclitaxel does not alter the Five Choice Serial Reaction Time Task, a test which requires rats to respond to visually presented stimuli[11] and vincristine does not alter sensorimotor gating.[10] However, repeated injections of a combination of methotrexate and 5-fluouracil impaired sensorimotor gating five weeks later[13] suggesting different agents under different dosing regimens may alter this type of sensory processing. Platinum analogs cisplatin and carboplatin compromise cochlear function as measured by death of cochlear outer hair cells and increases in auditory brainstem responses.[14,15] The agent 5-fluorouracil produces a progressive change in auditory brainstem response after 1, 7, 14 and 56 days of treatment as indicated by increases in inter-peak latency values. These changes are indicative of myelin damage or myelin loss which translates to longer latencies of impulse transmission (conduction).[16] The findings that particular cancer chemotherapeutic agents may alter sensory processing could potentially impact cognitive functioning or at least the rate at which stimuli are encoded.

Effects of Cancer Chemotherapeutic Agents on the Disruption of Motor and Spontaneous Behavior in Animal Models

If cancer chemotherapeutic agents either increase or decrease motor behaviors, this effect would impact the results of learning and memory assays. In a study of drug combinations, rats received methotrexate, the steroid prednisolone, or combinations of two agents at doses below those causing neurotoxicity. A number of core behaviors such as stand, sit, rear, walk, lying-down as modified by groom, head turn, look, smell, sniff and no activity were recorded by video and scored. Sex-, dose-dependent and interaction-effects were observed for three clusters of spontaneous behavior (behavioral initiations, behavioral total time and behavioral time structure). The combination of methotrexate and prednisolone had generally greater deleterious effects on behavior than did the same agents administered singly. The female rats were more sensitive to single agents or the combination than were the male rats. Interestingly, the effects of the drug combinations were dose-dependent, that is, some combinations were antagonistic, whereas others were neutral or synergistic demonstrating the need to study multiple dose combinations.[17] In another study of spontaneous behavior, a single injection of 250 mg/kg methotrexate in rats impaired novel-object preference without a difference in total exploration time.[18] However, a combination of 37.5 mg/kg methotrexate and 75 mg/kg 5-fluorouracil in mice failed to alter preferences for a novel object. These mice showed more total object exploration time during training and testing, suggesting that the mice were impaired during the memory phase of the experiment or that the mice were more aroused by the novel environment and therefore habituation to the environment was delayed.[13] These three studies demonstrate that cancer chemotherapeutic agents, especially in combinations, can alter normal motor or spontaneous behaviors and this potential should be controlled for during experiments examining the effects of these agents on learning and memory.

Effects of Cancer Chemotherapeutic Agents on Motivational Behavior in Animal Models

Because cancer chemotherapeutic agents produce emesis in patients,[19] there is a question in rodent studies of whether these agents may produce conditioned taste aversion or perhaps produce alternations in motivation. Hypothetically, if a chemotherapeutic agent that produces nausea was injected prior to or after access to a novel solution, the animal may avoid the novel solution because a Pavlovian association between the solution and the nausea has been made. Indeed, in traditional conditioned taste aversion assays, the lithium chloride is injected immediately after the exposure to the novel flavor.[20] In a two-day autoshaping procedure, 75 mg/kg 5-fluorouracil injected *immediately after* the acquisition session failed to alter responding the next day for a novel solution in mice (Walker, unpublished observations). If this dose of 5-fluorouracil produced nausea and conditioned taste aversion, the mice would still avoid the novel Ensure solution and a retrieval deficit would be observed on Day 2. Doses of methotrexate sufficient enough to cause 23% mortality were administered to neonatal Sprague-Dawley rats and then the surviving rats were tested two weeks later in two conditioning assays. In this test, methotrexate impaired the ability of lithium chloride to establish a conditioned taste aversion and further disrupted conditioned emotional responses assays. These effects were independent of sensory deficits, motor impairment, or histopathology.[21] However, when the conditioned taste aversion test included a feature-negative discrimination task, methotrexate failed to alter conditioning in Lewis rats although the mortality rate was only 2% in this study.[22]

The reinforcing or motivational efficacy of a reward can be measured by a progressive ratio assay. In this task there are two measures of reinforcing efficacy: breakpoint and response rate. The breakpoint is defined as the ratio at which the subject stops responding or the highest ratio completed if a time-constrained session is used.[23,24] Therefore, lower breakpoint values indicate lower reinforcing value for a reward. In our laboratory, we assessed whether 75 mg/kg 5-fluorouracil alone or in combination with 3.2 mg/kg methotrexate would attenuate motivation for a palatable food reinforcer (Ensure) as measured by a progressive ratio schedule of reinforcement in Swiss-Webster mice. In these studies, the mice were food-restricted and trained to nose-poke reliably in an operant experimental chamber, approximately 1-2 weeks and then the ratio requirement was increased on a log progressive schedule (1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 52 ...).[25] The effects of the these two cancer chemotherapeutic agents on breakpoints or the highest ratios completed for two consecutive days were compared to responding on the previous saline test day. Interestingly, 75 mg/kg 5-fluorouracil alone or in combination with 3.2 m/kg methotrexate failed to change either breakpoint responding or rates of responding for Ensure on either on the day of injection or the day after the injections suggesting that these doses are not behaviorally suppressive or toxic.[6] Therefore, the Ensure solution appeared as efficacious a reinforcer whether or not 5-fluorouracil alone or in combination with methotrexate was injected. The conditioned taste aversion studies and the progressive ratio studies suggest that at least for 5-fluorouracil and perhaps methotrexate motivational responding is not dramatically impacted by administration of these agents.

Acute Effects of Cancer Chemotherapeutic Agents on Learning and Memory in Animal Models

Only a few reports exist in the literature of preclinical studies that test the effects of chemotherapeutic agents on learning behavior in rodents despite the potential clinical impact of this research question. However, some cancer chemotherapeutic agents have been tested in traditional learning and memory assays. For example, cyclophosphamide produced transient memory deficits in a mouse step-down inhibitory avoidance-conditioning task without impairments in open field behavior or locomotion.[26] Similarly, the selective estrogen receptor modulators, or antiestrogens, tamoxifen and toremifene produce memory impairments in mice. Without affecting locomotor activities, tamoxifen decreased escape latency, toremifene increased the number of errors in two passive avoidance tasks and both compounds delayed latencies in an appetitively-motivated

T-maze.[5] In another study, tamoxifen impaired retrieval but not acquisition of spatial information processing in the Morris water maze.[27] These data suggest that tamoxifen may affect memory consolidation and retrieval whereas toremifene may also impair acquisition, thus underscoring the importance of examining multiple compounds in tests that measure acquisition, consolidation, retrieval and retention.

A simple model that is particularly valuable for studying the effects of cancer chemotherapeutics because it incorporates several aspects of learning and memory is called 'autoshaping'. In the first description of autoshaping, the repeated pairing of a light stimulus with the delivery of food eventually led to the emergence of a response from pigeons that could be differentiated and maintained by its consequences.[28] The autoshaping task combines both Pavlovian and instrumental conditioning and requires an intact neuronal system, specifically the hippocampus, septum and cortex.[29-31] A particular advantage of the autoshaping test is that it is sensitive to deficits produced by drugs of varied pharmacological classes on the acquisition and/or the retention of a response and the drugs can be administered at various time points before learning or acquisition on Day 1, after acquisition of the task on Day 1 and/or before retrieval on Day 2.[32] Impairment is reflected as an increase in four different behavioral measures relative to saline-treated control groups on any one of two days: (a) an increased adjusted latency to earn 10 rewards; (b) a decrease rate of responding for the rewards; and (c) the inclusion of a general activity rate measure to evaluate the potential for the disruption of discriminative control and the locomotor effects of a drug on behavioral responding. In a two-day variation of an autoshaping procedure, increased latencies to respond for 10 rewards and decreased response rates were observed on Day 2 after the administration of 5-fluorouracil, carboplatin and certain combinations of 5-fluorouracil with methotrexate prior to learning the autoshaping task on Day 1. Therefore, these agents altered the learning processes more heavily reliant on hippocampal functioning (consolidation, retrieval) than those less dependent on hippocampal functioning (acquisition) without altering overall locomotor or motivational effects[6] (Walker, unpublished observations). However, cyclophosphamide and high doses of tamoxifen disrupted acquisition of the autoshaped responding and impacted general activity rate suggesting the disruptive effects of cyclophosphamide and tamoxifen may be more behaviorally toxic than more subtle effects on learning and memory observed with 5-fluorouracil and carboplatin (Walker, unpublished observations).

It is possible that the effects of the cancer chemotherapeutic agents in the autoshaping task on Day 2 retrieval of the autoshaped responding could be due to state-dependent learning. The phenomenon of state-dependent learning refers to the retrieval of information acquired in the same context or physiological state that was present when the organism learned or encoded the task.[33] Therefore, the mice may not respond quickly or with high rates on the second day of an autoshaping task because the mice are responding in the task under a different context or physiological state (no chemotherapeutic agent) than when the mice learned the task on Day 1 (presence of chemotherapeutic agent). To address this question, we tested 75 mg/kg 5-fluorouracil in a state-dependent learning design. In four separate groups of mice, we injected: (1) saline prior to the Day 1 and Day 2 sessions (Sal-Sal); (2) 5-fluorouracil prior to the session on Day 1 and saline prior to the session on Day 2 (5FU-Sal); (3) saline prior to the session on Day 1 and 5-fluorouracil prior to the session on Day 2 (Sal-5FU); and (4) 5-fluorouracil prior to the Day 1 and Day 2 sessions (5FU-5FU). Analysis of variance indicated that the timing of the 5-fluorouracil injection impacted performance on Day 2 ($F_{(4,30)} = 9.75$, $p < 0.003$) but not Day 1. Specifically, the effects of 75 mg/kg 5-fluorouracil significantly impaired Day 2 retrieval relative to all other groups only when injected prior to the Day 1 session suggesting the occurrence of acquisition and/or consolidation disruption (Fig. 1). The fact that we observed retrieval deficits on Day 2 in the 5FU-Sal and 5FU-5FU groups but a lack of retrieval deficits for the mice that received 75 mg/kg 5-fluorouracil prior to the session on Day 2, the Sal-5FU group, suggests that state-dependent learning is probably not the predominant learning phenomenon impacted by this agent. Otherwise, deficits in 5FU-Sal and Sal-5FU groups would have represented a drug state change. Additionally, the fact that Day 2 performance for the Sal-5FU group was not significantly different from Day 2 performance for the

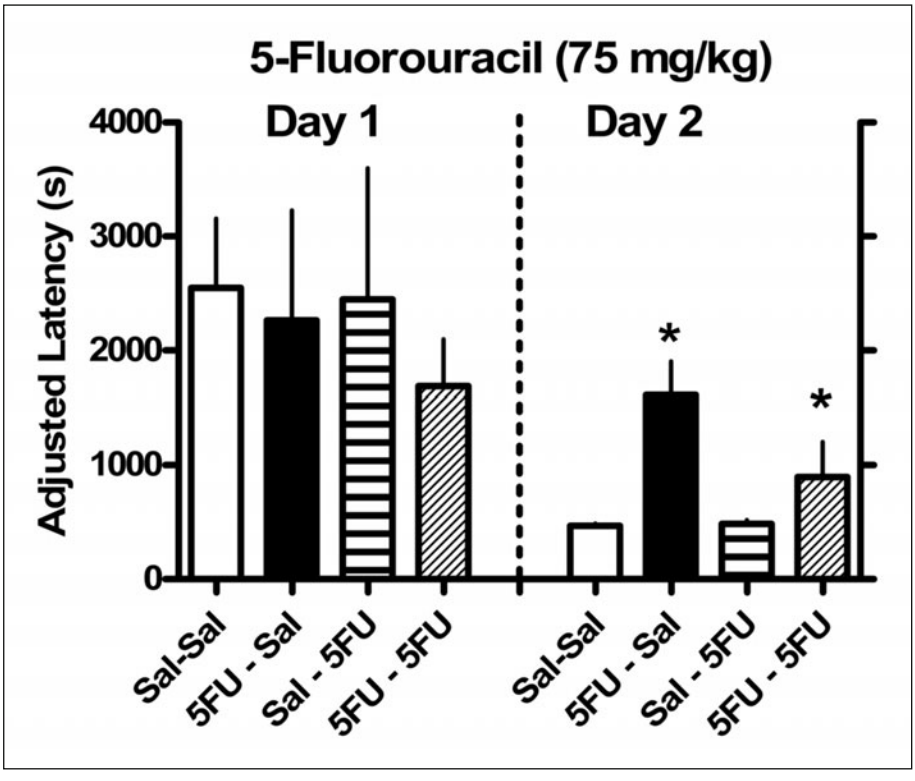

Figure 1. Effects of saline and 75 mg/kg 5-fluorouracil on learning and memory processes dependent on injection timing. Ordinate: Adjusted latency (latency to 10th reinforcer—latency to 1st reinforcer). Abscissa: saline prior to the Day 1 and Day 2 session (Sal-Sal, N = 12); 5-FU prior to the Day 1 session and saline prior to the session Day 2 (5FU-Sal, N = 6); saline prior to the Day 1 session and 5-FU prior to the Day 2 session (Sal-5FU, N = 5); 5-FU prior to the Day 1 and Day 2 sessions (5FU-Sal, N = 6). *$p < 0.001$ for 5FU-sal and $p < 0.05$ for 5FU-5FU. Vertical bars represent S.E.M.

Sal-Sal control group suggests that 5-fluorouracil is not interfering with the retrieval of previously learned responses. In summary, the deficits observed for 5-fluorouracil on Day 2 retrieval measures in the autoshaping do not appear to be a result of state-dependent learning.

Repeated Treatment of Cancer Chemotherapeutics in Animal Models

Rarely would an individual receive a single dose of chemotherapy to treat cancer in a clinical setting. Therefore, animal models of chemotherapy-induced learning deficits should incorporate a repeated treatment regimen and that regimen should approximate the kinds of doses that would be administered to humans. Actually most preclinical studies in animal models involve more than one injection of the cancer chemotherapeutic agent under study. For example, in a conditioned avoidance test, i.c.v. (intracerebroventricular) methotrexate injections on three alternative days produced impairments of both learning and memory in young rats.[34] In another set of experiments, groups of mice received three weekly injections of 37.5 mg/kg methotrexate and 75 mg/kg 5-fluorouracil and were tested in a battery of learning and memory tasks in a Morris water maze. After repeated methotrexate and 5-fluorouracil administration, mice exhibited deficits in tests of spatial memory, nonmatching-to-sample learning and delayed-nonmatching-to-sample learning that

correspond to the susceptibility of the frontal lobes and hippocampus to these agents. There were no changes noted in cued memory or a discrimination learning tests[7] that correspond to caudate nucleus and related striatal structures.[7,35] During and after 4 consecutive weeks of a combination of 37.5 mg/kg methotrexate and 75 mg/kg 5-fluorouracil, whole-brain event-related potentials were recorded in mice in a paired-click paradigm and contextual fear conditioning. These mice showed impaired sensory gating 5 weeks after the drug treatments began and demonstrated increased freezing during fear conditioning suggesting either the memory phase of the experiment was impaired or that the mice were hypersensitive to the environmental stimuli.[13] Similarly, rats treated with three weekly treatments of a combination of cyclophosphamide and doxorubicin showed impairments in contextual but not cue-specific fear responses suggestive of potential of hippocampal neurotoxicity.[36]

However, not all repeated treatment regimens of cancer chemotherapeutic agents result in learning or memory impairments. Repeated injections of 80-100 mg/kg cyclophosphamide or 150 mg/kg 5-fluorouracil were administered to rats at 0, 2, 8, 12, 18 weeks and then tested an additional 7, 16, or 29 weeks after the last drug treatment. In this study, cyclophosphamide caused a transient *enhancement* of both memory and hippocampal synaptic plasticity in spatial learning tasks.[37] Similarly, repeated treatments of paclitaxel for 5 days failed to alter reaction time, correct responses, or the percentages of omissions or intertrial interval responses in a Five-Choice Serial Reaction Time Task despite the fact that this paclitaxel regimen produces an increased sensitivity to mechanical stimuli.[11]

Potential Neural Mechanisms of Chemotherapy-Induced Learning and Memory Impairments

A series of studies in humans have been published suggesting that cancer chemotherapeutic regimens can produce both structural and functional changes in various brain regions such as the prefrontal cortex, parahippocampus and perhaps striatal structures that are correlated to various deficits in cognitive functioning.[38-40] In the Morris water maze and novel object recognition task, rats treated with methotrexate showed deficits correlated with decreased hippocampal cell proliferation suggesting impairments of spatial memory and comparator functions of the hippocampus, respectively.[18] The susceptibility of hippocampal regions to chemotherapeutic agents is further supported by in vitro immunocytochemistry and immunofluorescence studies that begin to define a cellular basis for deficits observed in these learning and memory assays. Even at doses below or at standard chemotherapeutic clinical regimens, carmustine, cisplatin, methotrexate, thioTEPA and cytarabine produce increased cell death and decreased cell division in the subventricular zone, in the dentate gyrus of the hippocampus and in the corpus callosum of mice and rats.[3,18,41] The observation that chemotherapeutic agents are more toxic to the cells responsible for hippocampal neurogenesis than to cancer cell lines suggests that learning and memory deficits could be detected even at doses below those normally used in chemotherapeutic regimens.

Similarly, at or below clinically relevant exposure levels, 5-fluorouracil produced toxicity to central nervous system progenitor cells and nondividing oligodendrocytes in vitro and in vivo. Both acute damage and a delayed syndrome of increasing damage to myelinated tracts were associated with altered transcriptional regulation in oligodendrocytes and myelin pathology. This occurred with only transient effects on brain vasculature endothelial cell apoptosis and inflammation suggesting the mechanism of pathology is more likely oligodendrocyte death and a loss of the progenitor cell population required for replacement of these cells. Furthermore, a regimen of 1, 7, 14 and 56 days of 5-fluorouracil produces a progressive change in auditory brainstem response indicative of myelin damage or myelin loss.[16] Finally, based on the capacity of estrogens to increase hippocampal dendritic spines[42] and the potential of chemotherapeutic agents to induce early menopause in female cancer patients,[2] synergistic impairments would likely be observed when chemotherapeutic agents are administered to female patients in combination with the antiestrogens especially on consolidation and retrieval tasks.

Conclusion

In summary, a preclinical literature is emerging that indicates cancer chemotherapeutic agents can produce various impairments in sensory processing, acquisition, consolidation and retrieval in rodent animal models of learning and memory. As more studies examine cancer chemotherapeutic agents alone and in combination during repeated treatment regimens in a range of assays, the animal models will become more predictive tools for the assessment of these impairments and the underlying neural mechanisms. These kinds of preclinical investigations in conjunction with clinical assessments will enable physicians to make informed choices about therapeutic regimens for their patients and may lead to alternative or complementary therapies that reduce or eliminate chemotherapy-induced cognitive deficits.

Acknowledgements

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Chapter 19

Chemo Brain (Chemo Fog) as a Potential Side Effect of Doxorubicin Administration:
Role of Cytokine-Induced, Oxidative/Nitrosative Stress in Cognitive Dysfunction

Christopher D. Aluise, Rukhsana Sultana, Jitbangjong Tangpong, Mary Vore, Daret St. Clair, Jeffrey A. Moscow and D. Allan Butterfield*

Abstract

Doxorubicin (ADRIAMYCIN, RUBEX) is a chemotherapeutic agent that is commonly administered to breast cancer patients in standard chemotherapy regimens. As true of all such therapeutic cytotoxic agents, it can damage normal, noncancerous cells and might affect biochemical processes in a manner that might lead to, or contribute to, chemotherapy-induced cognitive deficits when administered either alone or in combination with other agents.

Introduction

In 1980, Dr. Peter Silberfarb and colleagues reported cognitive changes in patients undergoing chemotherapy treatments. Twenty-two men and twenty-eight women were included in this study with malignancies such as respiratory, digestive, Hodgkin's disease, leukemia and multiple myeloma. It was reported that, overall, patients scored significantly worse on various tests of cognition and recall after undergoing chemotherapy.[1] Interestingly, cognitive decline was evident in patients not receiving chemotherapy directed at the central nervous system (CNS); this was surprising, due to the fact that a majority of the drugs administered in this study are known to not cross the blood brain barrier (BBB). This report was the first to observe that drug penetration of the brain parenchyma is seemingly not a requirement for cognitive dysfunction resulting from nonCNS-directed chemotherapy.[1]

Memory impairment as a result of brain radiation or CNS-directed chemotherapy is a well-established and universally accepted consequence of these treatment options. However, cognitive defects resulting from chemotherapeutic agents known specifically not to cross the BBB is a less understood phenomenon. As a result, there is still some debate over the validity of declining brain function as a direct side effect of chemotherapy. Emotional factors, such as anxiety and depression, that are consequences of cancer diagnosis and treatment, are likely to contribute to deficits in memory and cognition. Nevertheless, multiple reports find significant association of chemotherapy with instances of memory impairment, even after methodological or statistical

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adjustments for fatigue and other mental issues.[2-6] Therefore, the potential exists for a peripherally confined chemotherapeutic agent to cause CNS toxicity.

Due to the increasing survival of cancer patients after cancer therapy, the consequences of cognitive changes resulting from chemotherapy is receiving more attention. At present, the terms chemo brain or chemo fog have been adopted to describe the hazy mental state experienced by some patients after cancer treatment. Commonly described symptoms of chemo fog include lack of concentration, forgetfulness, dizziness and recall difficulty, although long term memory loss has not been observed.[7-12] Due to lack of consistent neuropsychological testing and statistical considerations, observations of chemo fog symptoms have been variably reported.[13] However, a majority of studies have noticed one or more cognitive domains are adversely affected after treatment, although some reports detect changes shortly after chemotherapy that eventually stabilize.[1-5,7,8,10,11,14-18] Some reports detail cognitive changes observed ten years after cessation of chemotherapy.[16]

Of the reports on chemotherapy-induced cognitive changes in humans, the most frequently documented class of patients is breast cancer survivors.[2-5,19,20] Therefore, routinely administered drugs for the treatment of breast carcinoma deserve investigation as a possible CNS toxin, irrespective of potential to cross the BBB. Along these lines, recent evidence suggests that anthracyclines are one of the commonly linked drug classes to changes in cognition; one of the most widely prescribed anthracyclines, doxorubicin (DOX), is frequently administered to breast cancer patients in standard chemotherapy regimens. Although the toxicity of several organs as a result of DOX is well established, the effect of DOX on brain is less understood and more complex, in part due to the inability of this drug or its metabolites to penetrate the CNS parenchyma. This chapter examines DOX-related CNS toxicity as a prototype anticancer agent relates to chemo fog as well as possible preventative therapies.

Description of DOX and Mechanisms of Action

DOX (Fig. 1) is one of several commonly used anthracyclines, a name given to drugs that originate from *Streptomyces* bacteria. DOX is mainly administered for the suppression of solid

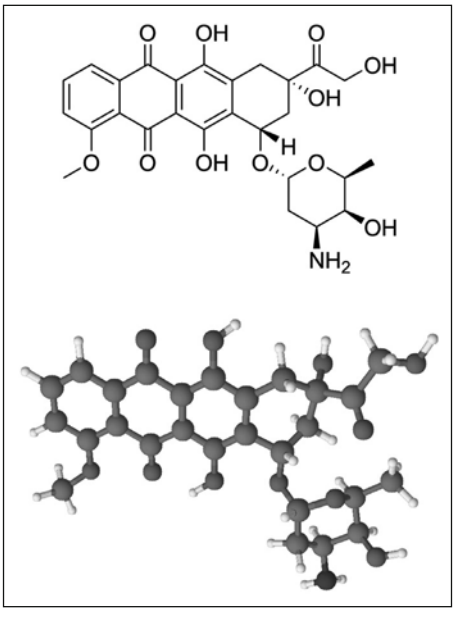

Figure 1. Chemical structure of doxorubicin,(8S,10S)-10-(4-amino-5-hydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione.

tumors but can also be useful to treat other types of cancer such as Hodgkin's disease, nonHodgkin's lymphoma and leukemia. DOX, like all cytotoxic chemotherapy, can damage normal, noncancerous tissues and therefore has a narrow therapeutic window. The acute toxicity of DOX includes nausea, vomiting, hair loss and suppression of the bone marrow. In addition to acute toxicity, DOX has cumulative dose-dependent cardiac toxicity that limits the total amount of DOX that can be given to a patient. DOX also is known to have hepatic and renal toxicity. Nevertheless, DOX is routinely administered under close surveillance to cancer patients because it is highly active in many malignancies.

The mechanism of DOX action is thought to be three-fold, creating debate in regard to how this drug kills cancerous cells in vivo. The prevailing paradigm of DOX action is intercalation into cancer cell DNA, thus inhibiting replication and tumor growth.[21-23] DOX has also been implicated to as a topoisomerase II poison,[24,25] which would serve to inhibit the DNA unwinding steps for cancer cell replication and transcription, leading to double strand breaks.[26,27] In addition, DOX can generate large amounts of reactive oxygen species (ROS), which may be lethal to tumors but may also be the source of nonspecific cellular toxicity. Oxidative stress has been detected in the hearts of rodents treated with DOX,[28-30] which may reflect an underlying cause of cardiotoxicity that limits its usage in patients.

Toxicity of DOX

Peripheral Oxidative Stress

DOX is a quinone-containing molecule and is capable of producing large amounts of free radicals via *redox cycling*. In this mechanism, the quinone moiety in DOX first undergoes a one-electron reduction to generate a semiquinone intermediate (Fig. 2). In biological systems, DOX can interact with several oxidoreductases such as NADPH dependent cytochrome P450 reductases,[31-33] NADH dehydrogenase (complex I)[34] and cytosolic xanthine oxidase,[35,36] all of which are capable of converting DOX to a semiquinone radical via one electron reduction. Interaction of DOX semiquinone with molecular oxygen converts the semiquinone back to the quinone producing superoxide (O_2^-) as a byproduct.[37,38] The increased production of free radicals can induce oxidative modifications of proteins, lipids, nucleic acids and carbohydrates, adversely affecting biomolecular function.[39] The increased production of ROS by DOX redox cycling is manifested by increased protein oxidation, lipid peroxidation, DNA/RNA oxidation, advanced glycation end products and reactive nitrogen species (RNS).[40-42] As a matter of fact, almost 50% of chemotherapeutics currently administered to patients are quinone-containing compounds[43] and may have similar oxidative effects as those of DOX.

The O_2^- radical released during the semiquinone-to-quinone conversion of DOX can react with nitric oxide to form peroxynitrite ($ONOO^-$), a highly reactive RNS. Peroxynitrite has a half-life of less than a second and can undergo a variety of chemical reactions depending upon its cellular environment, the presence of CO_2 and the availability of reactive targets, forming modifications such as 3-nitrotyrosine (3-NT). Tyrosine residues in a protein are critical sites for posttranslational modifications (PTM) such as phosphorylation. Hence, this modification may prevent necessary PTMs, thereby hindering various signaling pathways.[44] Another type of protein modification is the formation of protein carbonyl groups, which can be introduced into proteins by direct oxidation of certain amino acid side chains, peptide backbone scission, by Michael addition reactions with alkenal products of lipid peroxidation, or glycooxidation.[45,46] Both protein carbonyls and 3-NT are used as markers for assessing protein damage, as both oxidative modifications generally lead to a decrease in protein function/activity. In the periphery, DOX has been shown to increase the levels of these and other oxidative stress markers in plasma,[47] heart,[28-30] kidney,[48,49] liver[49] and testes.[50] Furthermore, co-administration of antioxidant compounds with DOX affords protection from these oxidative modifications in vivo.[47,49,51]

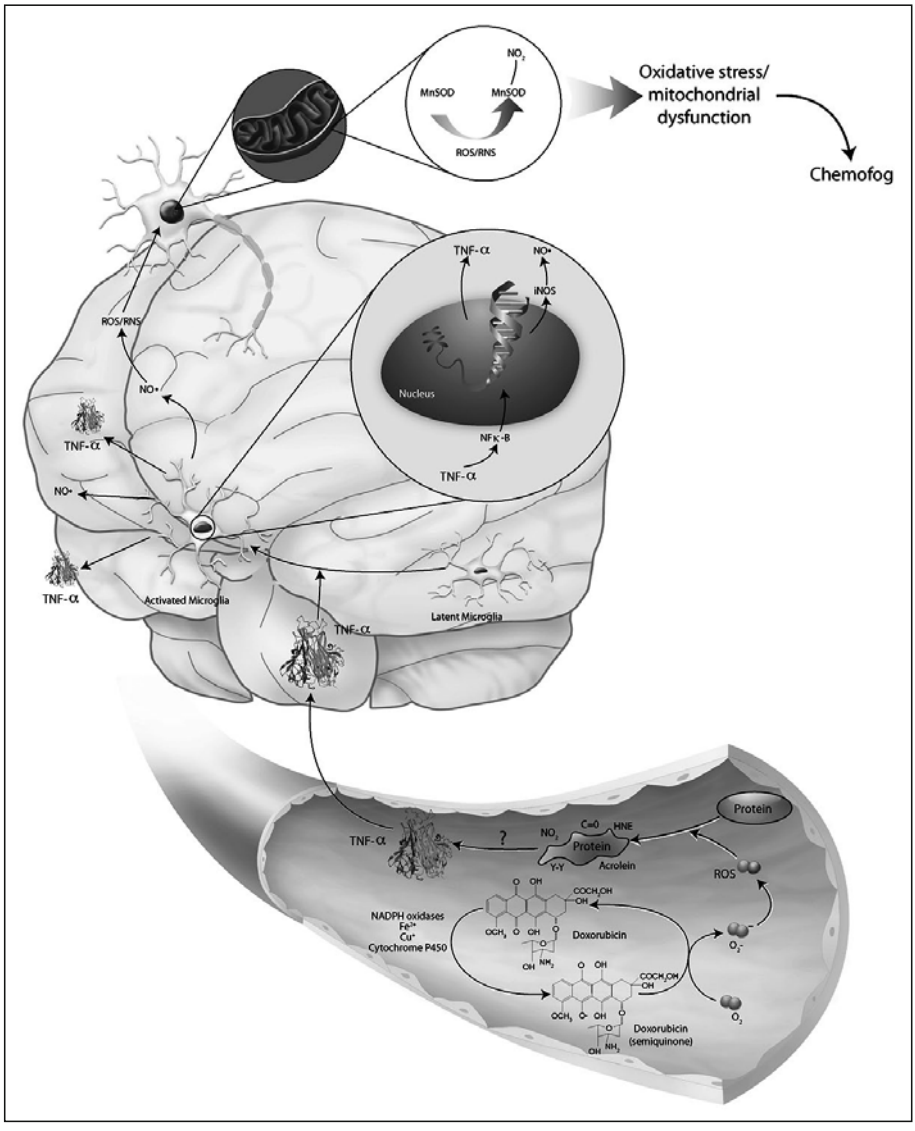

Figure 2. Authors' illustration summarizing the postulated physiological pathways that might link doxorubicin and chemo fog.

DOX and Central Nervous System Oxidative Stress

Although the aforementioned pathways of ROS/RNS interplay (downstream of O_2^- formation by DOX) are valid for any biological system, the introduction of free radicals in brain as a result of DOX is different in the CNS compared to the periphery, due to the purported inability of DOX to cross the BBB, although it may be possible for DOX to enter the brain area outside BBB. Therefore, the potential exists for an indirect mechanism of CNS oxidative toxicity as a result of DOX, one that does not necessarily involve redox cycling within the CNS. Although presently unclear, recent studies suggest that the mitigator of brain toxicity as a result of DOX

may be cytokine related (see next section). Oxidative stress has been detected in brains of mice treated i.p. with DOX and will be reviewed here.

Increased levels of protein oxidation, protein nitration and lipid peroxidation have been observed in brains from DOX-treated mice, indicative of oxidative stress that we hypothesize is related to chemo fog in humans.[40,51-53] Because oxidative stress is largely considered a cellular imbalance of oxidants and antioxidants, studies have shown that DOX also leads to depletion of CNS antioxidants, rendering cells vulnerable to these deleterious modifications.[51,53] Cardoso et al found that subchronic subcutaneous injections of DOX to Wistar rats lowered reduced glutathione (GSH) content in brain but increased vitamin E, possibly reflecting an oxidative stress defense reponse.[53] Co-administration of N-acetylcysteine (NAC), a GSH precursor capable of crossing the BBB, with DOX resulted in improvements in behavior relative to DOX-treated rats alone.[54] Another GSH precursor, gamma glutamylcysteine ethyl ester (GCEE), prevented DOX-induced oxidative stress in brain, further supporting our hypothesis that increasing endogenous brain-resident GSH may prevent chemo fog symptoms.[51]

DOX has also been observed to cause mitochondria-localized changes in brain. DOX lowered activity of brain aconitase, a mitochondrial tricarboxylic acid cycle enzyme, possibly via oxidative damage of this protein.[53] Alterations in mitochondrial levels of nitrated proteins were also observed with DOX treatment.[52] In the same study, MnSOD, another mitochondrial-localized enzyme that converts O_2^- to H_2O_2, was observed to be nitrated with i.p. administration of DOX.[52] As a result, the activity of MnSOD was observed to be decreased in brain mitochondria with DOX treatment.[52] Dysfunction of this protein could have disastrous consequences leading to buildup of mitochondrial O_2^- that could eventually culminate in cell death. Interestingly, changes in mitochondrial nitration were not observed in inducible nitric oxide synthase (iNOS) knockout mice with DOX treatment, implicating this enzyme in DOX-related oxidative damage to brain mitochondria.[52]

Role of Cytokines on Doxorubicin-Induced CNS Toxicity

Chemotherapy and chemotherapy-related neurotoxicity are associated with the release of proinflammatory cytokines. Cytokines are signaling molecules activated in response to infection or injury that trigger inflammation. In the CNS, cytokines also have roles in dopamine and serotonin metabolism, neural repair and neuronal/glial cell modulation.[12] Although inflammation and cytokine release is the body's primary defense against pathogen invasion, prolonged activation of these pathways can have adverse effects on the brain, resulting in fatigue, lack of motivation and appetite, as well as disturbances in sleep and concentration. It is generally accepted that cytokines in the blood can cross the BBB,[55,56] so that modulation of the levels of cytokines in the periphery, in principle, can mitigate the aforementioned brain effects.[43,56,57]

Cancer and chemotherapy are known to cause increases in circulating cytokine levels, which may be one mechanism by which cognitive impairment is manifested in these patients.[43,57,58] Meyers et al 2005 found that patients with acute leukemia had elevated levels of circulating cytokines before treatment, which correlated with the extent of cognitive impairment and fatigue.[58] Disruptions in cytokine levels have also been observed in neurodegenerative diseases such as Alzheimer disease (AD), multiple sclerosis and Parkinson disease (PD).[59] Clear associations between cytokines and cognitive dysfunction have been reported with immunotherapy administration, which resulted in depression, weakness and fatigue, in addition to cognitive decline.[60]

As noted, DOX cannot cross the BBB, as it has not been detected in areas protected by the BBB such as the cortex and the hippocampus.[57,61] However, DOX administration causes increases in levels of peripheral cytokines that are able to cross the BBB and stimulate local cytokine production,[62,63] inflammation and oxidative stress, leading to CNS toxicity. Increased levels of circulating tumor necrosis factor alpha (TNF-α) and TNF-α in the cortex and the hippocampus have been detected in mice treated intraparetoneally (i.p.) with DOX.[57,64] TNF-α in brain can activate glial cells to initiate local production of TNF-α,[65] which in turn induces nitric oxide synthase, leading to the overproduction of RNS.[66] Co-administration of DOX with an antibody against TNF-α quenches the aforementioned effects, further implicating this particular cytokine in DOX-related CNS toxicity.[57]

Evidence of Cell Death in Brain with DOX

Cell loss is intimately related to neurodegenerative disorders such as AD, a condition that in its earliest stages may share commonalities of pathology and symptoms with chemo fog. Because neurons are postmitotic cells, neuronal apoptosis is generally an irreversible event and could heavily contribute to a chemo fog-like condition in patients. The latter point is still debatable, because chemo fog symptoms are possibly transient,[12] while AD is an irreversible condition; however, cancer survivors are more predisposed to AD later in life,[67] so the possibility of neuronal death with a compensatory response of other neurons is also feasible. Magnetic reasonance imaging studies demonstrated that chemotherapy for breast cancer led to lower white and grey matter volumes.[68,69] Administration of DOX is reported to affect levels of brain-localized apoptotic markers in vivo, further supporting the role of cell death in chemo fog.[57]

Disturbances in mitochondrial respiration can lead to apoptotic cell death. Tangpong et al reported decreased mitochondrial respiration 3 hours after i.p. administration with DOX.[57] Treatment of mice with DOX increased levels of pro-apoptotic proteins Bax and p53, as well as the levels of anti-apoptotic Bcl-XL, in brain mitochondria.[52] Bax is capable of forming complexes with p53 and inducing permeability of the outer mitochondrial membrane, leading to cytochrome c release;[70] this complex was detected in brains of DOX-treated mice, along with elevated cytosolic levels of cytochrome c.[52] DOX has also been shown to increase susceptibility of brain mitochondria to permeability transition pore (PTP) opening induced by Ca^{2+}.[53] Brain changes as a result of DOX are likely due to TNF action, as co-administration of DOX with TNF antibody abrogated TNF levels in brain and mitochondrial toxicity.[52] During apoptosis, cytochrome c release to the cytosol leads to a series of reactions that activate caspase 3 to initiate programmed cell death; increased caspase 3 activity was detected as early as 3 h and as long as 72 h in brain after i.p. treatment of mice with DOX. Increased levels of TUNEL positive cell death were also observed in brains of DOX-treated mice, consistent with results discussed above.[52]

Description of Chemo Fog in Context of DOX

The terms "chemo fog" or "chemo brain" have been currently adopted to describe the cognitive decline experienced by some patients after cessation of chemotherapy. Such symptoms can last for at least 10 years following cessation of therapy.[16] After treatment, noticeable differences in memory, executive function, attention/concentration and processing speed are commonly described.[12] Of these symptoms, memory changes are the most frequently documented, particularly in studies of breast cancer patients.[7,10,71] Coincidentally, breast cancer patients are commonly treated with anthracyclines such as DOX to suppress tumor growth. Rodents treated with DOX (in addition to cyclophosphamide) displayed deficits in hippocampal-related learning and memory.[15] Memory impairment has also been demonstrated in rats treated with DOX as evidenced by passive avoidance testing.[54] Patients treated with DOX and cyclophosphamide displayed lower overall cognitive scores and visuospatial skill, although this report found increases in executive function after chemotherapy.[72] In general, the cognitive changes resulting from chemotherapy are relatively mild compared to other memory impairments, such as AD. Also unlike AD, data suggest that this side effect may not be permanent. Nevertheless, even temporary cognitive alterations are capable of negatively affecting patient quality of life.[73]

As mentioned previously, peripheral administration of DOX causes biochemical changes such as increases in peripheral inflammatory cytokines (TNF-α) and oxidative stress,[47,52,57] brain oxidative damage,[40,51,54] mitochondrial impairment[53] and depletion of CNS antioxidants,[51,53] potentially leading to neuronal death and observed defects in memory.[15,54] Furthermore, cotreatment of DOX with brain accessible antioxidants has resulted in improvements in memory,[54] correlating with preservation of the oxidative status of the periphery and CNS.[47,51,52] Therefore, the presence of oxidative damage in brains of subjects treated with DOX may mimic the early stages of AD, which has overwhelming evidence of brain-resident oxidative stress and impairments in working memory. However, co-administration of antioxidants with DOX in cancer patients has been met with some resistance in the oncology community, as ROS generation is one of several hypothesized

mechanisms by which DOX is lethal to tumors. However, Wang et al found that DOX induces apoptosis differently in tumor cells than normal cells; detoxification of H_2O_2 in tumor cells does not affect DOX-induced apoptosis, in stark contrast to normal epithelial cells.[74]

Chemo fog patients complain of having to exert more cognitive effort for everyday tasks after chemotherapy compared to before treatment.[43] In correlation with this statement, breast cancer patients 5-10 years after cessation of chemotherapy were observed to have lower resting brain glucose metabolism, along with a greater modulation of blood flow in the frontal cortex and cerebellum during a short-term memory recall test (compared to healthy controls);[16] results of this study imply that affected areas of the brain must work harder to function normally during testing, in turn utilizing more glucose, compared to control subjects. Because glyoclytic, TCA and electron transport enzymes are susceptible to oxidative damage in the presence of increased free radicals,[40,52] the possibility exists for free radical damage to enzymes involved in glucose metabolism as an indirect result of DOX, eventually leading to clinical observations of memory impairment. Because ATP is the end product of glucose metabolism, oxidative damage to glycolysis-related pathways would decrease metabolic efficiency, resulting in higher amounts of glucose needed to maintain basal ATP levels. Decreased cellular ATP could disrupt ion channels, namely the Na+/K+ ATPase and Ca^{2+} in neurons, resulting in cognitive dysfunction; this is purely speculative, however and requires more study to be decisively concluded. Nevertheless, oxidative damage and changes in glycolytic metabolism can both result in cell death, either in concert or independently, which would heavily contribute to symptoms of chemo fog.

Conclusion

Five-year survival rates for the treatment of breast cancer are approximately 80% in the United States[75] and much of this demographic group were at one point treated with anthracyclines such as DOX. Although the primary objective of chemotherapy is improved survival, it is imperative to also preserve the quality of life of the patient as best as possible. While the efficacy of DOX cannot be ignored, this drug has been linked to toxicity in several organs including heart and brain, the latter described in this chapter. Recent research shows that chemo fog experienced by a fraction of cancer survivors treated with drugs such as DOX may be a result of cytokine elevation in the periphery which migrates across the BBB to induce inflammation/oxidative stress leading to cell death. Figure 1 illustrates our model. This mechanism of toxicity is somewhat different from the DOX-related toxicity of other organs that are not protected by the BBB. This side effect of chemotherapy is receiving more attention as the number of cancer survivors continues to rise. Ultimately, any alteration to chemotherapy regimens to address the issue of chemo fog will have to be rigorously tested to ensure that these precautions do not compromise drug efficacy against tumors. Studies to further elucidate DOX- induced chemo fog are currently in progress in our laboratories.

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Chapter 20

Effects of 5-FU

Peter M. Wigmore,* Sarah Mustafa, Maha El-Beltagy, Laura Lyons, Jariya Umka and Geoff Bennett

Abstract

5-fluorouracil (5-FU) is a chemotherapeutical agent used to treat cancers including breast and colorectal. Working as an antimetabolite to prevent cell proliferation, it primarily inhibits the enzyme thymidylate synthase blocking the thymidine formation required for DNA synthesis. Although having a relatively short half-life (<30 mins) it readily enters the brain by passive diffusion. Clinically, it is used both as a single agent or in combination with other chemotherapies and has been associated with the long-term side effects of cognitive impairment, known as "chemo brain" or "chemo fog". These accounts have come primarily from patients undergoing treatment for breast cancer who report symptoms including confusion and memory impairment, which can last for months to years. Psychometric studies of patients have suffered from confounding variables, which has led to the use of rodent models to assess the cognitive effects of this drug. Researchers have used behavioral and physiological tests including the Morris water maze, novel object location/recognition tests, shock motivated T-maze, sensory gating and conditioning, to investigate the effect of this drug on cognition. The variety of cognitive tests and the difference in dosing and administration of 5-FU has led to varied results, possibly due to the different brain regions associated with each test and the subtlety of the drug's effect, but overall these studies indicates that 5-FU has a negative effect on memory, executive function and sensory gating. 5-FU has also been demonstrated to have biochemical and structural changes on specific regions of the brain. Evidence shows it can induce apoptosis and depress cell proliferation in the neurogenic regions of the adult brain including the sub granular zone (SGZ) within the hippocampus and in oligodendrocyte precursor populations within white matter tracts. Furthermore, investigations indicate levels of doublecortin, a marker for newly formed neurons and brain derived neurotrophic factor, a cell survival modulator, are also reduced by 5-FU in the SGZ. Thus, 5-FU appears to have a lasting negative impact on cognition and to affect cellular and biochemical markers in various brain regions. Further work is needed to understand the exact mechanisms involved and to devise strategies for the prevention or recovery from these symptoms.

Introduction

Drug Action

5-fluorouracil (5-FU) (Fig. 1), a fluorinated analogue of uracil, was designed as an anticancer agent over 40 years ago and has continued to be widely used in the treatment of many cancers including breast and colorectal.[1] 5-FU works as an antimetabolite and its major site of action is the inhibition of the enzyme thymidylate synthase. After administration, 5-FU, is converted into several cytotoxic metabolites the most active of which is fluorodeoxyuridine monophosphate

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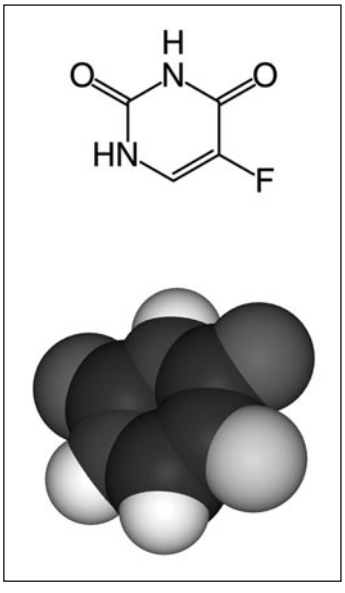

Figure 1. Chemical structure of 5-FU (5-fluoro-1H-pyrimidine-2,4-dione).

(FdUMP) which forms a covalent ternary complex with thymidylate synthase, blocking its action by preventing binding of its normal substrate.[2] The interaction between FdUMP and thymidylate synthase requires folate metabolites which can be augmented by administering folinic acid (leucovorin) with 5-FU, a protocol used in the treatment of colorectal cancers.[3,4]

Thymidylate synthase catalyses the conversion of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP) in the synthesis of the DNA base thymidine. Inhibition of thymidylate synthase reduces the thymidine formation required for DNA synthesis during cell proliferation and leads to an accumulation of dUMP. Subsequent metabolism of FdUMP produces compounds which can bind directly to DNA and this together with the incorporation of dUMP into newly synthesized DNA causes the formation of DNA strand breaks. A further metabolite of 5-FU, (FUTP) can be incorporated into RNA, producing cytotoxicity by interfering with RNA processing and function.[2,5-7]

5-FU has a short half life in serum (10-25 mins) in both humans and rodents and is broken down in the liver by the enzyme dihydropyrimidine dehydrogenase (DPD).[8-11] Thymidylate synthase activity can however take over 24 hours to return to normal after a single injection of 5-FU.[11,12] Patients deficient in DPD suffer from acute toxicity if treated with 5-FU.[13]

Clinical Usage

In adjuvant chemotherapy for breast cancer, 5-FU is used as part of a systemic poly-chemotherapy regime involving co-administration with other chemotherapy agents. The most common combinations are cylophosphamide, methotrexate and 5-fluorouracil (CMF), 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) or 5-fluorouracil, epirubicin and cylophosphamide (FEC).[14,15] 5-FU rapidly crosses the blood brain barrier by passive diffusion reaching concentrations in the CSF of between 11-50% of the serum concentration.[16,17] As might be expected from a drug able to access the brain, patients on 5-FU have on occasions presented with a variety of neurological symptoms including encephalopathy and cerebellar syndrome with ataxia and ocular problems but these usually resolve rapidly once drug treatment is stopped.[13]

Cognitive Effects

Reports of much longer lasting symptoms involving cognitive impairment which persist after the end of treatment have however been associated with chemotherapy involving 5-FU.[18-21] A small number of reports of 5-FU monotherapy have recorded deteriorations in cognition by patients[22-24] but most accounts have come from breast cancer patients who, as indicated above, are generally treated with 5-FU in combination with other chemotherapy drugs. Patient descriptions of their symptoms have led to the use of the terms "chemo brain" or "chemo fog".[25] Symptoms include confusion and memory impairments which have a significant impact on quality of life and ability to return to work.[25] This has led to a large number of investigations of the phenomena using psychometric testing of patients, not all of which have been able to demonstrate a significant effect of chemotherapy on cognition. However a series of meta analyses have concluded that a significant number of patients experience a mild to moderate effect on spatial and verbal memory and executive function.[25-27] Controversy exists as to the proportion of patients who experience chemo brain and the duration of the effect. Some studies have found deficits persisting for years while others find that test results return to normal within 12 months.[18,28] Finding suitable controls to compare with patients undergoing chemotherapy has been a problem and more recent studies have found

Table 1. Animal models of the effects of 5-FU on cognition

	Species	Drugs	Dose	Delivery	Tests and Results
Foley et al 2008	Mouse	MTX 5-FU	3-32 mg/kg 3-75 mg/kg. Singly or together	Ip single Injection	Increased latency in conditioning. Synergistic effect when drugs given together.
Han et al 2008	Mouse	5-FU	40 mg/kg	Ip 3 injections every 2nd day	Transient increase in apoptosis, prolonged reduction in proliferation in neurogenic regions and white matter tracts. Myelin pathology. Auditory impairments.
Mustafa et al 2008	Rat	5-FU	25 mg/kg	Iv 5 injections over 12 days	Deficits in NOL test. Reduced DCX and BDNF.
Gandal et al 2008	Mouse	MTX 5-FU	37.5 mg/kg 35-75 mg/kg	Ip each week for 4 wks	Impaired auditory gating. No effect in NOR or CFC tests.
Lee et al 2006	Rat	5-FU Cylophos-phamide	150 mg/kg 100 mg/kg	Ip 4 injections over 18 wks	Improved water and T maze at 8-10 wks. Impaired LTP during but improvement after drug administration.
Mignone and Weber 2006	Mouse	5-FU Thio TEPA	50 mg/kg 1-10 mg/kg	Ip 3 daily injections	Proliferation reduced by thioTEPA, unaffected by 5-FU.
Wincour et al 2006	Mouse	5-FU MTX	75 mg/kg 37.5 mg/kg	Ip 3 weekly injections	Reduced performance in Morris Water Maze test.

NOL: Novel object location; NOR: Novel object recognition; CFC: Contextual fear conditioning; DCX: Doublecortin; BNDF: Brain derived neurotrophic factor; LTP: Long term potentiation.

cognitive impairments in patients prior to chemotherapy.[29] For this reason animal studies, which avoid the confounding variables associated with differences in treatment and disease, have been used to asses the cognitive effects of chemotherapy agents (Table 1).

Animal Models

All animal studies on the effects of 5-FU have used rodents, for whom a number of behavioral and physiological tests are available to measure different aspects of cognition. Recognition and spatial working memory can be measured using the novel object recognition (NOR), novel object location (NOL) tests,[30,31] the Morris water maze and T maze.[32,33] As a reduction in spatial memory is one of the cognitive deficits described by chemotherapy patients,[34] these tests have been popular in testing for the effects of chemotherapy in animal models. The NOL test requires the animal to remember the relative position of two identical objects while the NOR test keeps the objects in the same position but changes the appearance of one of the objects after an initial exposure. Both tests make use of the exploratory interest shown by rodents to novel changes in their environment. Untreated animals spend significantly more time examining objects in a new location (NOL) or with a novel appearance (NOR) from that seen previously. Spatial and recognition memory are a particular function of the hippocampal formation and both tests require an intact hippocampus with the NOL specifically requiring an intact dentate gyrus.[35] The NOR test is similar but is thought to involve both hippocampal and cortical input.[35] We have found deficits in the performance of the NOL test after treatment of rats with 5 injections of 5-FU over 12 days. Treated animals fail to discriminate between objects in novel or familiar locations.[36]

In contrast mice treated with a combination of methotrexate (MTX) and 5-FU given as 4 injections over 4 weeks, showed no deficits when tested with the NOR test.[37] It is likely that differences in species, drug combination; drug delivery and the behavioral test used underlie this difference but it also indicates that the memory deficits produced are subtle and may be picked up by some tests and not others.

The Morris water maze tests spatial memory by requiring animals to memorize the location of a submerged platform within a circular pool. In the shock motivated T maze, animals have to learn to make alternative left and right turns to avoid foot shock. Two groups have used one or both of these tests to investigate the effects of 5-FU administration on spatial learning. Mice receiving 3 weekly injections of 5-FU in combination with MTX were tested in variations of the water maze.[38] Those variations which tested spatial memory, showed a small but significant deficit in drug treated animals which made more errors and took longer to find the submerged platform.[38] In investigations by the second group,[39] 5-FU or cyclophosphamide was administered to rats (5 injections, each given every 4 weeks) which were allowed to recover for 7 weeks or 29 weeks. Surprisingly both 5-FU and cyclophosphamide treated groups showed improved performance compared to controls in both the water and T maze tests at the shorter time interval but were indistinguishable from control animals at the later time point. Comparison between this and other studies is made harder by the different drug combinations and the timing of the behavioral tests used. Lee et al[39] also tested hippocampal long term potentiation (LTP) in slices of hippocampus from animals put down either during cyclophosphamide treatment or at 7 or 53 weeks. LTP, a measure of synaptic plasticity believed to underlie memory formation, was reduced in animals during drug administration, but paralleling some of the behavioral results, showed improvement at 7 weeks which persisted at 53 weeks.

A further test of the cognitive processing ability of different brain regions (auditory and frontal cortices, thalamus and possibly hippocampus) is provided by measures of auditory sensory gating.[40] This describes the process by which the brain reduces its response to a subsequent auditory stimulus. With electrodes implanted in the CA3 region of the hippocampus, mice treated with 5-FU and MTX showed decreased gating indicating a reduced ability to filter auditory input.[37] This deficit has been found as a cognitive affect in patients in a variety of situations including breast cancer patients treated with chemotherapy.[41]

The effects of 5-FU or MTX given either singly or in combination have been tested on mice using a test of the conditioned association between an auditory stimulus and liquid reward.[42] Mice received a single injection of the drug(s) prior to acquisition training on day one and were then tested on day two for the latency and accuracy of their responses to the auditory stimulus. Drug treatment did not significantly affect acquisition of the learnt response and MTX on its own did not produce significant effects on the following day. In contrast the highest dose of 5-FU produced increased latencies when the animals were tested the following day. Interestingly combinations of low doses (but not high doses) of MTX with 5-FU also produced deficits indicating an interaction at particular dose combinations. These results indicate a deterioration in the retrieval and retention of a learnt response, an effect probably involving both hippocampal and other cortical areas.

Brain Regions Associated with the Behavioral Effects of 5-FU

Spatial memory tasks in particular involve the hippocampal formation but it is likely that chemotherapy induced cognitive impairments involve other brain regions. Variations of the water maze task in which animals have to remember and discriminate between cues indicating the location of the platform require frontal lobe input. Mice treated with both MTX and 5-FU showed deficits in this task indicating that activity of both hippocampus and frontal cortex was impaired by chemotherapy treatment.[38]

Contextual fear conditioning (CFC) pairs an unpleasant stimulus (foot shock) with a particular location or context (test chamber). Learning this association requires input from both hippocampus, amygdala and cingulate gyrus.[43-45] Treatment of mice with both 5-FU and MTX showed no impairment in learning this association.[37] However in our hands (unpublished results) rats treated with a course of 5-FU injections show significant impairment in CFC as indicated by a reduced response to the test box in comparison with control animals 24 hours after training. The CFC test is thought to be a good measure of declarative memory[46] one of the cognitive domains in which patients report a decline.[34]

Biochemical and Cellular Markers of the Effects of 5-FU Chemotherapy

As well as behavioral testing, investigations of specific biochemical and structural changes in hippocampus and other brain regions, after 5-FU treatment, have carried out. Of particular interest is the impact of 5-FU on regions of the brain which continue to produce neurons throughout life. These adult neurogenic regions include the sub granular zone of the dentate gyrus within the hippocampus, which continues to add granule cell neurons to the dentate gyrus.[47] The addition of these cells has been shown to be important to hippocampal function and to be required in the recall and consolidation of memory.[48] A second neurogenic region, the sub ventricular zone (SVZ), in the lateral walls of the lateral ventricles contributes inter neurons to the olfactory bulbs.[49] As chemotherapy agents are designed to kill dividing cells it is likely that systemic administration of these compounds will reduce cell proliferation and neurogenesis in these regions. This question has been addressed by a number of groups using animal models of 5-FU toxicity (Table 1).

Several investigations have shown that low doses of 5-FU are particularly toxic to neural and oligodendrocyte progenitor cells in vitro.[50,51] Extending these observations, Han et al[50] treated mice with a course of 3 injections of 5-FU, which significantly increased apoptosis in both neurogenic regions (SGZ of the dentate gyrus and SVZ of lateral ventricle) in the weeks after drug administration. Cell proliferation in these regions remained depressed for at least several months.[50] Work in our laboratory has also found that 5-FU inhibits proliferation in the SGZ (unpublished results) and this is associated with a reduction in doublecortin (DCX), a marker of newly formed neurons.[36] Reductions in cell proliferation in the SGZ are associated with cognitive impairments of hippocampal function[48,52] and provide a direct mechanism to explain some of the symptoms experienced by patients. However it is worth noting that other investigators have failed to show a significant decrease in cell proliferation in the SGZ with a similar dosing regime to Han et al[50] but with a smaller sample size.[53]

Treatment with 5-FU also reduces levels of brain derived neurotrophic factor (BDNF) in the hippocampus.[36] BDNF is not thought to be involved in the cell proliferation required for

neurogenesis in the hippocampus, but modulates cell survival and is required for LTP and memory consolidation.[54] A decrease in BDNF levels could provide an additional mechanism for the memory impairments experienced by patients on 5-FU.

5-FU has been reported to affect the white matter tracts of the CNS as visualized by MRI.[55,56] This was investigated by Han et al[50] in mice where it was found that 5-FU treatment induced apoptosis in these regions (corpus callosum) immediately after drug treatment followed by a prolonged period of reduced cell proliferation associated with demyelination, myelin pathology and an impairment in auditory conduction speed.[50] The extended time course of these effects mirrors the descriptions by patients on chemotherapy of prolonged effects after the cessation of drug treatment.

Conclusion

In summary, researchers have used a variety of animal behavioral tests to look of effects of 5-FU on cognition. Not all investigations have shown a deleterious effect of 5-FU, in fact one set of experiments showed an improvement. The remaining investigations however all show that 5-FU has a negative impact, producing deficits associated with memory, executive function and sensory processing which are similar to the effects described by patients on chemotherapy. Integration of the different animal studies is complicated by the different strains, species and dosing regimes used. Similarly the range of behavioral tests used makes comparison difficult but strengthens the conclusion that this drug has a robust effect on cognition which can be detected using a variety of behavioral paradigms. Several of the tests are thought to directly relate to cognitive deficits described by patients after chemotherapy and indicate that these symptoms can be brought about independently of the confounding variables noted in patient studies. Many of the behavioral tests employed require functions of the hippocampus, sometimes in conjunction with other brain regions such as the amygdala and frontal cortex. The hippocampus is involved in memory consolidation and recall and is one of brain regions which continues to generate new nerve cells throughout life. 5-FU treatment reduces neural progenitor cell proliferation and levels of the neurotrophic factor BDNF in the hippocampus, changes which are associated with a decline in memory. Animal studies of the effects of other chemotherapy agents have also found a reduction in cell proliferation in this region[53,57,58] suggesting that this may be a common feature of chemotherapy treatment. In addition changes to white matter tracts may also produce long lasting structural changes to the brain affecting neural processing and the speed of axon transmission. The effects of 5-FU treatment can occur rapidly but also may last for many months or longer. Further work will be needed to determine the exact cellular and molecular changes brought about by drug treatment, the interaction between drugs given in poly therapy and the time course of their effects. As it is becoming clearer that the cognitive effects of chemotherapy are real and specific to particular brain regions it should be possible to develop strategies for the prevention or recovery from these symptoms. Both pharmacological and other therapies have been suggested[59-63] and animal models of this condition provide a suitable method to test the efficacy of these approaches.

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Chapter 21

Future Directions

Robert B. Raffa* and Ronald J. Tallarida

Abstract

The chapters of this book summarize much of what has been done and reported regarding cancer chemotherapy-related cognitive impairment. In this chapter, we point out some future directions for investigation.

Background

Thanks to advances in prevention, early detection and treatment, an increasing number of patients are surviving cancer. In fact, for certain types of cancer, the majority of patients are surviving. They transition from being cancer patients to being cancer survivors. This is giving rise to a new and rapidly growing category of people within the healthcare arena. This is certainly terrific news. However, many survivors are reporting that they might be experiencing residual and lingering effects from having cancer, despite being cured of it. Just as they needed care as patients, they now need care as survivors—which has given rise to the new term and field of 'survivor care'.

A great deal of the improvement in outcome and increase in patient longevity is undoubtedly attributable to the cancer chemotherapeutic agents. There is no question that advances in the selection of drugs, dose regimens and specific combinations used to treat either the primary tumor or its spread, have extended lives. Patients, families, healthcare providers and others are grateful for these drugs that have helped to usher in an era of increased survival. But no drug lacks adverse effects. This is no less true for cancer chemotherapeutic drugs than it is for any other category of drugs and the treatment-related adverse effects of these drugs are well known. Cancer chemotherapeutic drugs are cytotoxic and they need to be in order to successfully bring about the desired therapeutic benefit. But this same property raises the possibility of undesired toxicity on normal cells. If such 'collateral' toxicity occurs to a sufficient extent, some unwanted damage might result—damage that outlasts the period of exposure and gives rise to chronic adverse effects.

The potential chronic adverse effects of cancer chemotherapeutic agents are less well known than are the acute adverse effects of these agents. But the increase in cancer survival rates has increased the awareness of the possible chronic effects of the agents. Given the known susceptibility of the nervous system to the toxic effects of many of the drugs that are typically used to treat cancer, it would not be surprising if some chronic effects of the drugs manifested themselves as impairments in certain aspects of cognitive function.

'Chemo Fog'/Chemo Brain: Current

What is known about chemo fog/chemo brain? Basically three very general things: (1) a significant number of cancer survivors who were given chemotherapeutic drugs, either individually or more commonly in combinations, both during their treatment and even years after the final treatment, report it; (2) some apparently well-designed studies, using a battery of standardized

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tests, detect deficits in the cognitive ability of these patients; and 3) some recent, apparently objective, imaging tests detect differences in the brain scans of these patients. Beyond this, little is known with certainty.

The condition has been consistently reported by a large number of patients, so it merits serious scrutiny and study. It is also important that patients, families, healthcare providers, insurers, employers and others have the best information possible to inform their individual and collective decisions. Negative consequences can result from either underestimating or overestimating the condition.

Chemo Fog/Chemo Brain: Future

In the Preface to this book, several statements and questions about the current state of knowledge regarding chemo fog/chemo brain were enumerated. They are repeated here as the basis for delineating some directions for future study:

- *It is not clear that chemo fog/chemo brain exists*
  In multiple places throughout this book there are caveats about the interpretation of the results from studies that assess cognitive function in cancer survivors. The major hurdle, of course, is that it is unethical to design the proper control arm (patients from which chemotherapy is withheld). Furthermore, it is extremely difficult to control for, or even to know, all the myriad of other factors that are involved in addition to the chemotherapy. Another problem is that survivors might be able to compensate for minor impairments during the testing procedure. Yet the same impairments might be more troublesome for their normal daily activities. Future effort should be directed at using better test instruments or testing under more relevant conditions. In this regard, imaging studies are providing some interesting new possibilities. They might be able to identify not only under-active brain region function in a particular subject, but might also be able to identify over-active (i.e., compensating) brain region function in the same individual. More such studies should be conducted in order to determine their full capabilities and limitations.
- *If it exists, it is not clear what caused it*
  This is perhaps the most difficult question of all. It is the most fundamental one, yet is the one that might never be answered to everyone's satisfaction. Given the constraints on doing the definitive clinical trial, there are too many uncontrolled variables. For example, early studies did not establish a pretreatment baseline of cognitive function. Subsequent studies that try to obtain this information also run into the methodological uncertainty of whether a newly-diagnosed cancer patient facing an uncertain future is capable of giving an accurate reading on cognitive ability when tested for research and not treatment, purposes. It is also rare for a cohort of patients, even if matched on demographic and other factors, to be treated with the identical chemotherapeutic agents, at the same dose, given in the same sequence, using the same combination, at the same time and in the absence of other drugs for the same or other conditions. Perhaps it is the cancer itself and not its treatment, that gives rise to some long-lasting impairment of cognitive function, or the attendant depression that is known to accompany cancer or almost any chronic health condition. Perhaps the impairment is the result of any number of other confounding issues related to the disease, its treatment, or its perception or psychological impact on the patient. Or perhaps it is due to normal progression in the life cycle such as aging, onset of menopause, etc.
- *If chemotherapy-induced, it is not clear which drug(s) or drug combination(s)*
  The choice of agent or combination of agents is a clinical issue, not research, one. It is typically customized to the individual patient and can and often does, vary during the course of treatment. This cannot be changed. Future work can be directed to utilizing or developing data-mining techniques that can extract information from across studies. Of course, on the one hand the results will be confounded by the different demographics, disease severity, etc. On the other

hand, faced with so many variables, the randomness of the influences across studies might actually be of benefit, assuming that the population size is sufficient.

- *No 'prophylactic' or 'treatment' is known*
  Our lack of an understanding of the cause or physiological mechanism that is responsible for cognitive impairment in chemo fog/chemo brain hampers the rational design of an appropriate pharmacologic prophylactic or treatment. Until the required information is obtained, symptomatic treatment should be studied. Several stimulant drugs or drugs that enhance concentration have been, or are being, tried. The results of these trials should be published, even if the results are negative. A variety of nonpharmacologic techniques to maintain or to improve memory are available, primarily targeted to Alzheimer patients and should be tested for their utility in chemo fog/chemo brain.
- *Most survivors adjust, while some have problems*
  This is an area that deserves further investigation and documentation using high-quality and evidence-based measures. Many survivors, thankful for life, do not wish to seem ungrateful or viewed as complainers (*you survived cancer, what's a little memory problem?*). In fact, most adjust quite well and do not rate cognitive deficits as significantly impacting their quality of life. But what if they self-select on this measure? What if they do not pursue (or withdraw from) careers, jobs, or important assignments because they think that they cannot handle them? What if employers, out of the same concerns, do not give them challenging opportunities (that might lead to promotions)? What is the view of insurance providers? All of these questions should be studied and the data made available. Another area in great need of study is the impact of chemo fog/chemo brain on spouses and other family members.

Conclusion

In this chapter we have highlighted some aspects of cancer chemotherapy-related cognitive impairment that warrant future exploration or more definitive study. Clearly this is only a partial list. Each chapter of this book has suggested, either explicitly or indirectly, a variety of issues requiring clinical or basic science investigation. At present, there are many more questions than there are answers. The answers are eagerly awaited.

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