

Minireview

How chemotherapy damages the central nervous system

Christina A Meyers

Address: Department of Neuro-Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 431, Houston, TX 77030, USA. Email: cameyers@mdanderson.org

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Abstract

Chemotherapy adversely affects cognitive function both acutely and chronically, but little is known about the underlying mechanisms. A new study shows that short-term chemotherapy causes not only acute injury to progenitor cells, but also delayed damage to myelin.

The successful management of many cancers has been achieved mainly by aggressive treatment. Chemotherapy is generally not very specific, and it puts normal tissues and organs at risk. Although the brain is given some protection from systemic treatments by the blood-brain barrier, it is increasingly recognized that many chemotherapeutic agents affect brain function by direct and/or indirect mechanisms. Thus, cancer patients can experience various adverse symptoms, including cognitive dysfunction. Cancer patients have always known that their cognitive function is less efficient during cancer treatment, although in the past it may have been attributed to other causes, such as stress or depression. Several studies over the past decade have shown that this is a real effect of the disease and of its treatment on brain function [1-3]. It is also increasingly clear that cognitive dysfunction persists in some individuals long after treatment is ended, and some patients never fully recover [3,4]. Persistent symptoms are a cause of considerable distress for individuals who cannot return to their previous academic, occupational or social activities, or who can do so only with significant additional mental effort. However, the mechanisms underlying the development of persistent cognitive dysfunction have not been identified.

Many of the preclinical studies so far have focused on the acute effects of chemotherapy on hippocampal function and on associated deficits in learning and memory [5-9]. However, cancer patients generally have problems with memory retrieval and executive function, not with consolidation of memories, a pattern that suggests that frontal-subcortical white matter networks are involved rather than the hippocampus. In a ground-breaking new study in *Journal of Biology*, Mark Noble and colleagues [10] have now found that therapeutic levels of 5-fluorouracil (5-FU), an agent widely used to treat breast and colon cancers, among others, is associated with progressive delayed damage to myelin. This series of experiments helps define the mechanisms that could underlie the cognitive problems cancer patients experience during treatment, as well as those that persist long after treatment is discontinued.

In a manner similar to their previous work with other anti-cancer drugs [9], the authors first examined the effects of clinically relevant doses of 5-FU on central nervous system (CNS) stem cells, lineage-restricted progenitor cells and differentiated cell types [10]. They also compared the effects with those on human umbilical vein endothelial cells and a variety of cancer cell lines. They found that progenitor cells

and nondividing oligodendrocytes were vulnerable, suggesting that 5-FU neurotoxicity was not limited to dividing cells. This toxicity was observed at lower concentrations than generally used in other studies.

The authors then examined the effects of 5-FU on adult mice. They found an acute, transient increase in apoptosis in several brain regions, which subsided 56 days after injection. They found a more persistent suppression of proliferation in regions of the brain where proliferation is essential to normal function (the subventricular zone, the dentate gyrus of the hippocampus and the corpus callosum), primarily in progenitor cells and oligodendrocytes. To determine whether these findings resulted in functional impairment, they investigated the auditory brainstem response in the mice at various times following treatment. Loss of myelin is known to increase the latency between specific peaks in the auditory brainstem response, reflecting slowing of the impulse conduction between the ear and the brain. Exposure to 5-FU caused a progressive increase in inter-peak latencies, consistent with developing myelin damage, whereas cochlear function was not affected.

To follow up on this indication that delayed white matter injury was the result of 5-FU exposure, Noble and colleagues [10] undertook a more systematic investigation of oligodendrocyte biology in the corpus callosum. They found extensive damage to myelin, altered transcriptional regulation in oligodendrocytes and extensive myelin pathology 56 days after exposure to 5-FU. In contrast, CNS inflammation and vascular damage, which have been widely speculated to be underlying mechanisms of delayed CNS injury, were acute rather than delayed and thus did not seem to be related to the delayed demyelination.

Other preclinical studies of chemotherapy-induced CNS injury

Previous studies have shown that various chemotherapeutic agents cause cognitive impairment, although the results are variable. Winocur *et al.* [5] found that a combination of methotrexate and 5-FU induced impairments in tests of spatial memory and other cognitive tasks in mice. Reiriz *et al.* [6] also reported transient acute memory impairment in mice treated with a single dose of cyclophosphamide. Adriamycin has been demonstrated to increase oxidative stress in the brain, which may lead to cell dysfunction or cell death and thus contribute to cognitive dysfunction [7]. Crandall *et al.* [8] reported that long-term exposure to 13-*cis*-retinoic acid, which is often used in chemotherapy regimens, was associated with decreased neurogenesis and cell proliferation in the hippocampus and subventricular zone, and with impaired spatial learning and memory in

young adult mice. Dietrich *et al.* [9] found that three widely used chemotherapy agents (carmustine, cisplatin and cytosine arabinoside) were more toxic to CNS progenitor cells and nondividing oligodendrocytes than to many cancer cell lines *in vitro*. They also found that the agents caused increased cell death and decreased cell division in the subventricular zone, the dentate gyrus of the hippocampus and the corpus callosum in mice. These effects were observed for weeks after drug administration ended.

In contrast, Lee *et al.* [11] found transient improvement in memory and synaptic plasticity in rats treated with cyclophosphamide or 5-FU 8 weeks after administration, but not 29 to 42 weeks later, when the treated rats performed no differently from controls. This group did, however, find impaired long-term potentiation (a phenomenon critical for learning) in hippocampal slices taken during cyclophosphamide treatment, whereas they found enhanced long-term potentiation in slices obtained 8 and 53 weeks after treatment [11]. Thus, some of the variability of the results in these studies may be related to the time points of evaluation (acute versus chronic toxicity), the different agents under study, and the specific animal or preclinical model that was utilized.

Clinical studies

The studies of Noble and colleagues [9,10] will directly affect clinical research into the pattern of cognitive dysfunction in cancer patients and the associated imaging and physiological results. The incidence of acute chemotherapy-related cognitive dysfunction ranges from 15 to 70% [3,12]. One trial found that 61% of women receiving 5-FU, doxorubicin and cyclophosphamide for breast cancer showed a decline in cognitive function while on treatment. The decline occurred most often in attention, learning and processing speed and was not related to mood, demographic characteristics, clinical features or baseline level of cognitive function [3]. Consistent with the findings of Noble and colleagues [10], 50% of the women had not recovered 1 year after treatment was discontinued [3]. Long-term cognitive impairments have also been reported in cross-sectional studies of patients 2-10 years after treatment ended [4,13,14].

The findings of Noble and colleagues regarding delayed white matter injury and associated functional impairment may provide a mechanistic basis for the results of studies in cancer patients. A recent study of breast cancer survivors 3-6 years after chemotherapy was completed found that patients had abnormalities in the processing of an auditory stimulus compared with controls [15]. Interestingly, all of the patients had received 5-FU as part of their treatment

regimen. Silverman *et al.* [16], using positron emission tomography, found alterations in resting metabolism and cerebral blood flow in the basal ganglia, inferior frontal gyrus and cerebellum during memory activation in women who had received chemotherapy 5-10 years earlier.

Anatomical studies have also found changes in cancer survivors treated with chemotherapy. Using magnetic resonance imaging, Inagaki *et al.* [17] found smaller gray and white matter volumes in multiple brain regions 1 year after treatment compared with controls, although this was not observed in a cohort scanned 3 years after treatment. The reduced volumes at 1 year correlated with poorer performance on cognitive testing. Gray and white matter volume loss and hippocampal atrophy have also been reported in association with some chemotherapeutic treatments [18-20]. However, these findings have not always been replicated, suggesting the need for further investigation [21].

The findings of Noble and colleagues [9,10] have greatly contributed to our understanding of the mechanisms of acute and, importantly, progressive and delayed injury to the brain from clinically relevant short-term exposure to a widely used chemotherapy agent. Furthermore, their results are consistent with the clinical syndrome commonly observed in patients. This important study [10] underscores the need for varied and appropriate preclinical models that assess both acute and progressive delayed CNS injury due to cancer treatment. The knowledge gained from this and other studies will guide the development of translational clinical research to protect the nervous system from injury, to better treat injury that has developed as a result of treatment, and to improve the overall quality of life of cancer patients.

References

- Alvarez JA, Scully RE, Miller TL, Armstrong FD, Constine LS, Friedman DL, Lipschultz SE: **Long-term effects of treatments for childhood cancers.** *Curr Opin Pediatr* 2007, **19**:23-31.
- Schagen SB, Muller MJ, Boogerd W, Mellenbergh GJ, van Dam FSAM: **Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients.** *J Natl Cancer Inst* 2006, **98**:1742-1745.
- Wefel JS, Lenzi R, Theriault R, Davis RN, Meyers CA: **The cognitive sequelae of standard dose adjuvant chemotherapy in women with breast cancer: results of a prospective, randomized, longitudinal trial.** *Cancer* 2004, **100**:2292-2299.
- Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Skalla K, Whedon MB, Bivens S, Mitchell T, Greenberg ER, Silberfarb PM: **Neuropsychological impact of standard dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma.** *J Clin Oncol* 2002, **20**:485-493.
- Winocur G, Vardy J, Binns MA, Kerr L, Tannock I: **The effects of the anti-cancer drugs, methotrexate and 5-fluorouracil on cognitive function in mice.** *Pharmacol Biochem Behav* 2006, **85**:66-75.
- Reiriz AB, Reolon GK, Preissler T, Rosado JO, Henriques JAP, Roesler R, Schwartzmann G: **Cancer chemotherapy and cognitive function in rodent models: memory impairment induced by cyclophosphamide in mice.** *Clin Cancer Res* 2006, **12**:5000.
- Joshi G, Sultana R, Tangpong J, Cole MP, St Clair DK, Vore M, Estus S, Butterfield DA: **Free radical mediated oxidative stress and toxic side effects in brain induced by the anti cancer drug adriamycin: insight into chemobrain.** *Free Radical Res* 2005, **39**:1147-1154.
- Crandall J, Sakai Y, Zhang J, Koul O, Mineur Y, Crusio WE, McCaffrey P: **13-cis-retinoic acid suppresses hippocampal cell division and hippocampal-dependent learning in mice.** *Proc Natl Acad Sci USA* 2004, **101**:5111-5116.
- Dietrich J, Han R, Yang Y, Mayer-Pröschel M, Noble M: **CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents *in vitro* and *in vivo*.** *J Biol* 2006, **5**:22.
- Han R, Yang YM, Dietrich J, Luecke A, Mayer-Pröschel M, Noble M: **Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system.** *J Biol* 2008, **7**:12.
- Lee GD, Longo DL, Wang Y, Rifkind JM, Abdul-Raman L, Mamczarz JA, Duffy KB, Spangler EL, Taub DD, Mattson MP, Ingram DK: **Transient improvement in cognitive function and synaptic plasticity in rats following cancer chemotherapy.** *Clin Cancer Res* 2006, **12**:198-205.
- Moleski M: **Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia.** *Arch Clin Neuropsychol* 2000, **15**:603-630.
- Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF: **Cognitive deficits after postoperative chemotherapy for breast carcinoma.** *Cancer* 1999, **85**:640-650.
- Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Green-dale GA: **Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen.** *J Clin Exp Neuropsychol* 2004, **26**:955-969.
- Kreukels BP, Hamburger HL, de Ruiter MB, van Dam FS, Ridderinkhof KR, Boogerd W, Schagen SB: **ERP amplitude and latency in breast cancer survivors treated with adjuvant chemotherapy.** *Clin Neurophysiol*, 2008, **119**:533-541.
- Silverman DH, Dy CJ, Castellon SA, Lai J, Pio BS, Abraham L, Waddel Petersen L, Phelps MR, Ganz PA: **Altered frontocortical, cerebellar and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy.** *Breast Cancer Res Treat* 2007, **103**:303-311.
- Inagaki M, Yoshikawa E, Matsuoka Y, Sugawara Y, Nakano T, Akechi T, Wada N, Imoto S, Murakami K, Uchitomi Y: **Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy.** *Cancer* 2007, **109**:146-156.
- Schneiderman B: **Hippocampal volumes smaller in chemotherapy patients.** *Lancet Oncol* 2004, **5**:202.
- Saykin AJ, Ahles TA, McDonald BC: **Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives.** *Semin Clin Neuropsychiatry* 2003, **8**:201-216.
- Madhyastha S, Somayaji SN, Rao MS, Nalini K, Bairy KL: **Hippocampal brain amines in methotrexate-induced learning and memory deficit.** *Can J Physiol Pharmacol* 2002, **80**:1076-1084.
- Yoshikawa E, Matsuoka Y, Inagaki M, Nakano T, Akechi T, Kobayakawa M, Fujimori M, Nakaya N, Akizuki N, Imoto S, Murakami K, Uchitomi Y: **No adverse effects of adjuvant chemotherapy on hippocampal volume in Japanese breast cancer survivors.** *Breast Cancer Res Treat* 2005, **92**:81-84.