Cancer Chemotherapy and Cognitive Function in Rodent Models: Memory Impairment Induced by Cyclophosphamide in Mice

To the Editor: The study by Lee et al. (1) is the first report on the effects of cancer chemotherapy on cognitive function in rodent models. Given the increasing concern about cognitive dysfunction in patients receiving chemotherapy, the development of animal models to characterize chemotherapy-induced cognitive impairment has been proposed as a priority for future research (2, 3). Unexpectedly, Lee et al. (1) found an enhancement of both memory and hippocampal synaptic plasticity following several weeks of treatment with cyclophosphamide in rats.

We too have used rodent models to investigate the cognitive effects of cyclophosphamide. In contrast to the findings reported by Lee et al. (1), we have observed a transient memory impairment following cyclophosphamide administration in mice. In our experiments, male CF1 mice (70–90 days of age) were trained and tested in step-down inhibitory avoidance conditioning, a type of emotionally motivated, hippocampus-dependent memory task where animals learn to associate a location in the training apparatus with a footshock. Inhibitory avoidance training was carried out as described previously (4). Either 1 day or 1 week before behavioral training, animals were given a systemic injection of cyclophosphamide (8, 40, or 200 mg/kg, i.p.). Control animals were injected with saline. Mice treated with cyclophosphamide at 40 or 200 mg/kg 1 day before training showed significant impairment of 24-hour memory retention when compared with control animals [mean ± SE retention test latencies (seconds) were 61.30 ± 20.93 in the control group, 80.91 ± 25.02 in the group treated with 8 mg/kg cyclophosphamide, 22.0 ± 12.02 in the group treated with 40 mg/kg cyclophosphamide, and 12.36 ± 2.87 in the group treated with 200 mg/kg cyclophosphamide; both Ps < 0.01 compared with the control group with two-tailed Mann-Whitney U tests; n = 10–11 animals per group]. There was no significant difference among groups in training performance [overall mean ± SE training trial latency (seconds) was 12.77 ± 1.46; P = 0.16]. A control experiment showed that cyclophosphamide did not affect open field behavior (4), indicating that the impairing effects of cyclophosphamide on inhibitory avoidance could not be attributed to drug-induced alterations in locomotion, motivation, or anxiety (data not shown). Systemic administration of cyclophosphamide (8, 40, or 200 mg/kg, i.p.) did not affect inhibitory avoidance memory when given 1 week before training (data not shown).

Our results show that a single administration of cyclophosphamide induces memory impairment in a mice model of aversive conditioning. Further studies are required to characterize cognitive deficits induced by cancer chemotherapy in animal models and investigate the mechanisms underlying the differential effects of cyclophosphamide on memory in different experimental paradigms.

André B. Reiriz
Faculty of Medicine,
University of Caxias do Sul
Caxias do Sul, Rio Grande do Sul,
Brazil

Gustavo K. Reolon
Thales Preissler
Joemerson O. Rosado
João António P. Henriques
Center for Biotechnology,
Federal University of Rio Grande do Sul,
Porto Alegre, Rio Grande do Sul,
Brazil

Rafaël Roesler
Gilberto Schwartsman
Graduate Program in Medical Sciences,
Faculty of Medicine,
Federal University of Rio Grande do Sul,
Porto Alegre, Rio Grande do Sul,
Brazil

References

In Response: In their Letter to the Editor, Reiriz et al. have questioned the generalization of results that we recently presented about a rodent model to assess cognitive impairments induced by cyclophosphamide and 5-fluorouracil (1). In our study, we evaluated the effects of chronic regimens of these two chemotherapeutic agents on performance of young and aged female F344 rats in two complex learning tasks, the Morris water maze and the Stone 14-unit T-maze. Both tasks involve multiple trials spread over several days and required the rat to learn and remember complex spatial relationships. Our results showed that, with 8 weeks of recovery from the chemotherapeutic regimens, rats treated with either cyclophosphamide (100 mg/kg) or 5-fluorouracil (150 mg/kg) surprisingly did significantly better than untreated controls in both learning tasks. However, after providing even longer periods of recovery, 29 to 42 weeks, we observed no significant differences
in maze performance between treated rats and controls. Thus, despite the toxicity of the regimens of cyclophosphamide and 5-fluorouracil as applied, the treatments produced a transient improvement in performance and, with longer periods of recovery, no long-term negative effects on cognition as measured by these tasks.

Additional support for this conclusion was provided in our electrophysiologic assessment of long-term potentiation as measured in a slice preparation taken from the brains of rats during and after cyclophosphamide treatment. In hippocampal slices recorded from rats after both 8 and 53 weeks of recovery from 18 weeks of cyclophosphamide treatment, we noted enhanced long-term potentiation. In contrast, we observed impaired long-term potentiation in slices obtained from rats during cyclophosphamide treatment (15 weeks).

Reiriz et al. have addressed a different question. Specifically, they assessed acute toxic effects of a single dose of a chemotherapeutic agent. Male CD-1 mice were given one injection of cyclophosphamide (8, 40, and 200 mg/kg) either 1 day or 1 week before testing in a step-down inhibitory avoidance task. This paradigm involves a one-trail task, which assesses the strength of the association made between the natural action of stepping down from a platform and a mild footshock as a negative reinforcement received after stepping onto the grid floor. Mice treated with either of the two highest doses showed impaired memory when evaluated 24 hours after acquisition training. In this situation, the mouse was returned to the platform after 1 day or 1 week, and the latency to step down onto the grid floor where it had previously received the mild footshock was recorded as the measure of memory. When mice were tested following 1 week of recovery from a single injection of cyclophosphamide, they showed no impaired memory at any dose. Thus, it would seem only that the acute effects of cyclophosphamide were associated with the memory deficit observed in mice in this simple learning task. This result is consistent with our finding of decreased long-term potentiation during cyclophosphamide therapy (1).

It is possible that noncognitive performance effects of acute treatment influenced the results of Reiriz et al. They did not report any data on toxicity, body weight changes, or food intake in these mice. Although the data were not provided, they did report that the cyclophosphamide treatment had no significant effects on open-field performance. Thus, they concluded that the performance differences could not be attributed to effects of the drug on locomotion, anxiety, and motivation. However, if the treatment was having untoward effects on performance in general, such as a malaise or fatigue, then the affected mouse might show a slower time in the initial step-down latency. If the median scores had been reported, they might show that the mice receiving the higher doses of cyclophosphamide were exhibiting longer latencies, thus indicating a noncognitive performance deficit. The authors should reveal these data.

As we discussed in our article, we agree with Reiriz et al. that additional studies using animal models of cognitive deficits induced by cancer chemotherapy are needed to clarify reports in the literature about this clinical problem. There is a critical lack of well-controlled studies in appropriate animal models. The results of Reiriz et al. examine acute rather than chronic toxicity of a cancer chemotherapeutic agent, and their results do not contradict any conclusion we reached about the behavioral toxicity of cyclophosphamide.

A fundamental problem in assessing chemotherapy-induced cognitive decline is that cognition declines with age in people who have not received chemotherapy [see Fig. 1 from the Baltimore Longitudinal Study of Aging (2)]. It is important that future studies attempting to measure and document treatment-related cognitive decline take into account that the baseline is not level; age-related cognitive decline also happens at a measured rate in people who do not receive cancer treatment. They just do not have chemotherapy to blame.

Garrick D. Lee
Donald K. Ingram
Laboratory of Experimental Gerontology, Intramural Research Program, National Institute on Aging, NIH, Baltimore, Maryland

Dan L. Longo
Laboratory of Immunology, Intramural Research Program, National Institute on Aging, NIH, Baltimore, Maryland

References

Fig. 1. Age-related decline in memory performance assessed as errors made on the Benton visual memory test as measured in healthy men and women in the Baltimore Longitudinal Study of Aging (2).
Cancer Chemotherapy and Cognitive Function in Rodent Models: Memory Impairment Induced by Cyclophosphamide in Mice


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/12/16/5000

Cited articles
This article cites 6 articles, 3 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/12/16/5000.full.html#ref-list-1

Citing articles
This article has been cited by 7 HighWire-hosted articles. Access the articles at:
/content/12/16/5000.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.