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Editorial

EDITORIAL

Understanding Longitudinal Changes in Cognitive Function in Lymphoma Patients: Where to Next?

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Cancer-related cognitive impairment (CRCI) is rated by cancer survivors as one of the most troublesome symptoms experienced, and one that affects many aspects of their life (1-3). Studies suggest approximately 30%-45% of solid tumor cancer survivors have cognitive impairment based on neuropsychological assessment after completing adjuvant chemotherapy (4,5), and approximately one-half report sustained cognitive symptoms that they perceive to be due to their cancer and/or cancer treatment (5-8). Most studies have been conducted in younger women who have had breast cancer (9), with a small number of studies in people with other solid malignancies (4,10). There are limited data in patients with hematological malignancies (11-16) and a lack of studies documenting the longitudinal changes in cognition experienced over the course of treatment for lymphoma.

In this issue of the Journal, Janelsins et al. (17) address this gap by providing longitudinal data showing adults with lymphoma, compared with age- and sex-matched controls without cancer, score statistically significantly lower on tests of verbal memory, attention, and executive function from prechemotherapy to postchemotherapy and 6 months after chemotherapy. The effect size estimates show mean changes of group differences in the mild-to-moderate range (0.2-0.5) for statistically significant objective neuropsychological tests. Lymphoma patients had higher rates of self-reported cognitive symptoms compared with controls at baseline and at each follow-up time point.

Several strengths of the study are worth noting. Well-validated assessments of cognition were used, including assessment of cognitive impairment via traditional paper-and-pencil neuropsychological tests, computerized and phone assessments, and report of cognitive symptoms. The large national sample of lymphoma patients (n = 248) was compared with a matched control group (n = 212) recruited from community settings (17). A control group assessed at the same time points was included to account for practice effect, which is improvement in performance because of test familiarity, even when alternative forms are used, with repeated measures design (18). People with lymphoma performed worse over time even with opportunity for practice effect, whereas the control group improved with repeated testing, suggesting practice effect. Mixed models were included for analysis with adjustment for a priori baseline covariates, including self-reported cognitive symptoms.

Baseline assessments commenced before receiving chemotherapy, with the advantage in the lymphoma population that the prechemotherapy (baseline) assessment is generally not confounded by recent surgery and anesthesia as occurs with individuals with solid tumors. Although no cognitive impairment on objective assessments was observed at baseline, the report of statistically significantly more cognitive symptoms compared with controls before treatment is consistent with the notion of a prodromal phase of cognitive impairment among cancer patients before diagnosis (19,20), though not all studies have found this (20). Janelsins et al. (17) suggest that the biology of lymphoma and other hematological malignancies may have a unique contribution to CRCI in addition to other predisposing factors. Self-reported cognitive function may also more readily capture cognitive failures as experienced by patients in daily life as opposed to the idealized assessment conditions used during objective neuropsychological assessments (21). However, from other studies we know that there is a strong association between fatigue, symptoms of anxiety and depression, and stress, and cognitive symptoms (4,7,18,21,22), and the baseline assessment would be soon after diagnosis when these symptoms are likely to be high.

This study offers a unique opportunity to consider gender effects. Paradoxically, women reported greater cognitive difficulties compared with men, whereas men exhibited greater impairment on objective assessment of cognitive function (17). In our longitudinal study of cognitive function in colorectal patients treated with and without chemotherapy, we found that more women experienced impaired cognitive function at all time points up to 2 years after treatment, but men were more

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likely to experience decline in cognitive function over time (4). The weak correlation between self-report and objective measures of cognitive function is well known (21). Understanding any potential differential impact on self-report and objective assessment due to gender warrants further investigation.

Some questions remain. Which domains of cognition demonstrate selective vulnerability among lymphoma patients is yet to be clearly determined. Results indicated impairment in verbal memory and executive function, but testing across different modalities (computerized, paper and pencil, and phone) produced variable results. Phone assessment seemed most sensitive, with cognitive difficulties observed on all but 1 of the phone-administered assessments at postchemotherapy and 6-month follow-up. This result is similar to that observed in breast cancer survivors using a similar design (23), where the authors suggested phone assessment may be particularly sensitive to deficits in attentional processing. This interpretation is interesting because tests considered to assess attention regardless of administration mode (including phone assessment) did not indicate strong deficits. The merit of different modes of cognitive assessment is yet to be established, but validating sensitive, brief, and accessible ways of assessing cognition is desirable to support large longitudinal studies monitoring cognitive function in survivors (19,21).

This rich dataset, combined with the breast cancer cohort (23), presents opportunities for further analysis and understanding. However, longer duration longitudinal assessment is needed, especially given the magnitude of cognitive symptoms increased across the course of treatment, and assessment of objective cognitive function indicated cognitive impairment was persistent at 6 months posttreatment. Longitudinal studies establishing the duration of cognitive impairment after cancer treatment, and whether difficulties resolve or worsen, are needed to understand the long-term survivorship impact.

Finally, what do these results mean for people with lymphoma and their treating physicians? Cognitive difficulties experienced before treatment should be considered by treating teams. This is particularly important considering the relatively young age of diagnosis of most individuals with lymphoma who are at their most productive in terms of family and career and can generally look forward to a long duration of survival. While preventative measures and rehabilitation treatments are being trialed, educating individuals with lymphoma about available information, resources, and support will better equip them to manage expectations on level of cognitive functioning and return to their previous roles.

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References

1. Lange M, Licaj I, Clarisse B, et al. Cognitive complaints in cancer survivors and expectations for support: results from a web-based survey. *Cancer Med*. 2019;8(5):2654–2663.
2. Klaver KM, Duijts SFA, Engelhardt EG, et al. Cancer-related cognitive problems at work: experiences of survivors and professionals. *J Cancer Surviv*. 2020;14(2):168–178.
3. Boykoff N, Moieni M, Subramanian SK. Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. *J Cancer Surviv*. 2009;3(4):223–232.
4. Vardy JL, Dhillon HM, Pond GR, et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. *J Clin Oncol*. 2015;33(34):4085–4092.
5. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry*. 2014;26(1):102–113.
6. Boscher C, Joly F, Clarisse B, et al. Perceived cognitive impairment in breast cancer survivors and its relationships with psychological factors. *Cancers (Basel)*. 2020;12(10):3000.
7. Dhillon HM, Tannock IF, Pond GR, Renton C, Rourke SB, Vardy JL. Perceived cognitive impairment in people with colorectal cancer who do and do not receive chemotherapy. *J Cancer Surviv*. 2018;12(2):178–185.
8. Schmidt JE, Beckjord E, Bovbjerg DH, et al. Prevalence of perceived cognitive dysfunction in survivors of a wide range of cancers: results from the 2010 LIVESTRONG survey. *J Cancer Surviv*. 2016;10(2):302–311.
9. Mayo SJ, Lustberg M, M. Dhillon H, et al. Cancer-related cognitive impairment in patients with non-central nervous system malignancies: an overview for oncology providers from the MASCC Neurological Complications Study Group. *Support Care Cancer*. 2021;29(6):2821–2840.
10. Treanor CJ, Li J, Donnelly M. Cognitive impairment among prostate cancer patients: an overview of reviews. *Eur J Cancer Care*. 2017;26(6):e12642.
11. Phillips KM, McGinty HL, Cessna J, et al. A systematic review and meta-analysis of changes in cognitive functioning in adults undergoing hematopoietic cell transplantation. *Bone Marrow Transplant*. 2013;48(10):1350–1357.
12. Williams AM, Zent CS, Janelsins MC. What is known and unknown about chemotherapy-related cognitive impairment in patients with haematological malignancies and areas of needed research. *Br J Haematol*. 2016;174(6):835–846.
13. Hoogland AI, Nelson AM, Gonzalez BD, et al. Worsening cognitive performance is associated with increases in systemic inflammation following hematopoietic cell transplantation. *Brain Behav Immun*. 2019;80:308–314.
14. Syrjala KL, Artherholt SB, Kurland BF, et al. Prospective neurocognitive function over 5 years after allogeneic hematopoietic cell transplantation for cancer survivors compared with matched controls at 5 years. *J Clin Oncol*. 2011;29(17):2397–2404.
15. Jones D, Vichaya EG, Wang XS, Sailors MH, Cleeland CS, Wefel JS. Acute cognitive impairment in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplant. *Cancer*. 2013;119(23):4188–4195.
16. Correa DD, Root JC, Baser R, et al. A prospective evaluation of changes in brain structure and cognitive functions in adult stem cell transplant recipients. *Brain Imaging Behav*. 2013;7(4):478–490.
17. Janelsins MC, Mohamed M, Peppone LJ, et al. Longitudinal changes in cognitive function in a nationwide cohort study of patients with lymphoma treated with chemotherapy. *J Natl Cancer Inst*. 2021.
18. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12(7):703–708.
19. Small BJ, Jim HSL. Understanding the time course of cancer-associated cognitive decline: does impairment precede diagnosis? *J Natl Cancer Inst*. 2020;112(5):431–432.
20. van der Willik KD, Hauptmann M, Jóźwiak K, et al. Trajectories of cognitive function prior to cancer diagnosis: a population-based study. *J Natl Cancer Inst*. 2020;112(5):480–488.
21. Costa DSJ, Fardell JE. Why are objective and perceived cognitive function weakly correlated in patients with cancer? *J Clin Oncol*. 2019;37(14):1154–1158.
22. Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C. Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review. *Cancer Treat Rev*. 2012;38(7):926–934.
23. Janelsins MC, Heckler CE, Peppone LJ, et al. Longitudinal trajectory and characterization of cancer-related cognitive impairment in a nationwide cohort study. *J Clin Oncol*. 2018;36(32):3231–3239.